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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

Effect of Thyroid Hormone on Circulation
Henry M. Thomas Jr.

Clinical Syndromes Produced by Isolated Dysfunctions of the Renal Tubule
Thomas Findley

Simple Tests of Renal Function in Health and Disease
I. A Reappraisal of Their Value in the Light of Serial Renal Biopsies
Robert M. Kark, Victor E. Pollak, John F. Soothill, Conrad L. Pirani, and Robert C. Muehrcke
II. Simple Tests of Renal Function: Healthy Subjects
Frederick Sargent II and Robert E. Johnson

Treatment of Hyperthyroidism with Individually Calculated Doses of I^{131}
Franz K. Bauer and William H. Blahd

Paroxysmal Nocturnal Hemoglobinuria
William Dameshek and Hugh Fudenberg

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Hereditary Hemorrhagic Telangiectasia in Three Families
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Tumor Implantation at Paracentesis Sites
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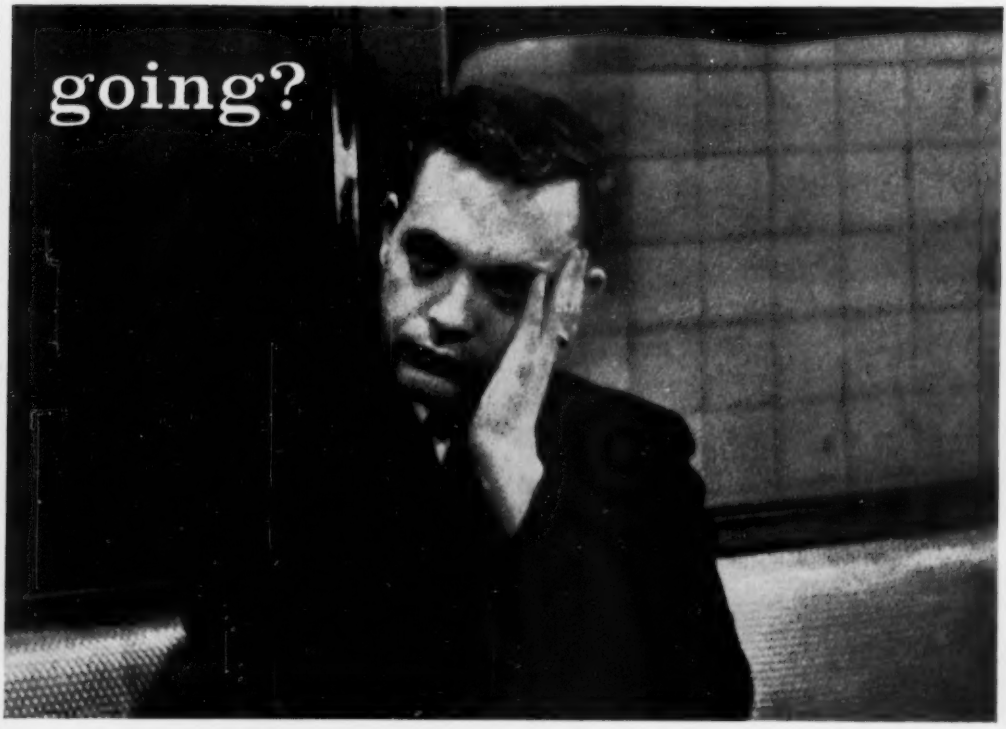

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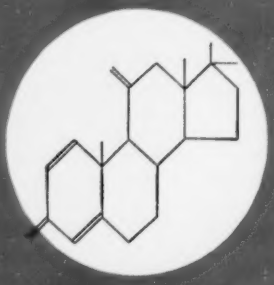

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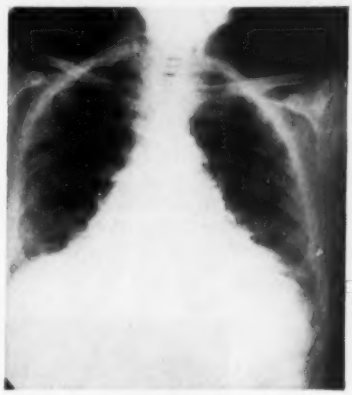

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1. Abramson, Julius; Bresnick, Elliott; and Sapienza, P.L.: *New England Jour. Med.*, 243:44, July 13, 1950.
2. Conybeare, John; and Mann, W.N.: Textbook of Medicine. Edinburgh, E. & S. Livingstone Ltd., 10th ed., 1952, p. 443.

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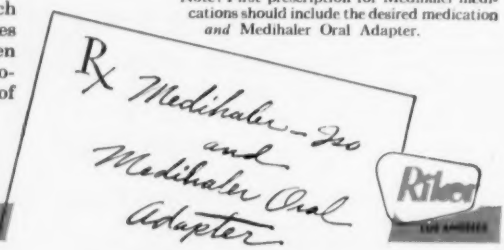

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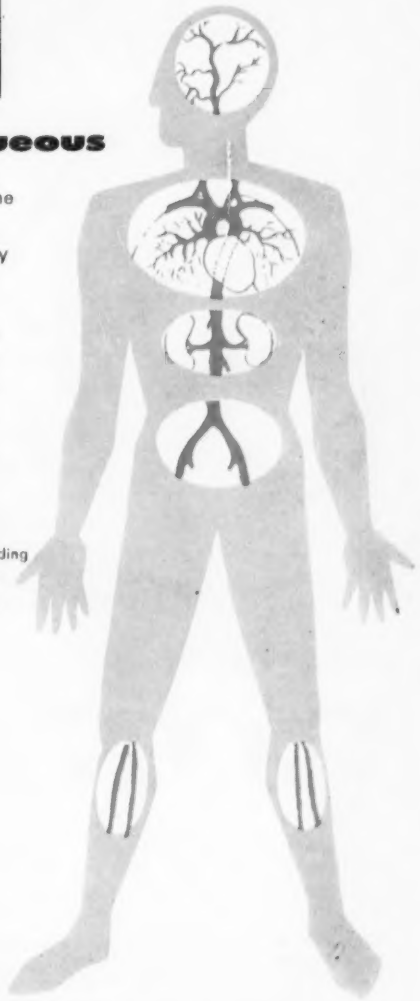

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Effect of Thyroid Hormone on Circulation

HENRY M. THOMAS Jr., M.D., Baltimore

Thyrotoxicosis is conspicuous because of its influence on the rate of the heart, and many of its most interesting symptoms originate in that organ. As early as 1786 Parry realized the connection between cardiac symptomatology and goiter, but to his mind the heart disease was the primary condition. He thought also that exophthalmos, which was present in his eight patients, was secondary to the heart disease. Even Graves, Stokes, and others in the mid 19th century were of the same opinion, and it was not until 1883 and 1885 that Kocher, and, independently, Horsley, recognized the part played in this syndrome by the thyroid hormone. In 1899 Kraus published in *Wiener klinische Wochenschrift* his concept of the so-called neurotic or thyrotoxic heart from which the current ideas have been developed.

At first, interest was centered entirely on the heart in hyperthyroidism. Did toxic diffuse (exophthalmic) goiter produce hypertrophy of the heart or merely dilatation? What, if any, were the gross and microscopic pathological changes in the heart? Years were spent studying hearts and heart muscle from patients with toxic diffuse goiter (Graves' disease) and from animals fed on thyroid extract. The results of all this work were largely on the negative side. Today few if any pathologists claim that prolonged excesses of thyroid hormone, whether endogenous or exogenous, cause visible microscopic changes in the myocardium. Dilatation of the heart is widely admitted, but proponents of work hypertrophy still lean on scanty evidence.

Later, as cardiological studies were extended to include determinations of blood pressure, blood volume, and blood flow, the circulatory changes were measured also in cases of thyrotoxicosis. Here the yield of interesting facts was good from the first and has continued to be so up to the present time. Recently much new information has been provided, but even today answers have not been agreed upon to such simple questions as: What is the mechanism in hyperthyroidism leading to tachycardia and subsequently to auricular fibrillation? Through what homeostatic mechanisms do the various circulatory changes develop?

When one examines a patient with pronounced thyrotoxicosis, after noting the exophthalmos, tremor, and signs of loss of weight, one is struck by evidence of involvement of the cardiovascular system.[1] In the neck one sees active pulsation in the carotid artery. The pulse is rapid, full, and bounding; the apex impulse is rapid and forceful and is apt to be felt slightly further toward the axilla than normally. At the apex the heart sounds are overactive, the first sound is loud and often abrupt, and there may be an apical systolic murmur and,

This paper is being published simultaneously in the *Journal of the American Medical Association*.

From the Department of Medicine, Johns Hopkins University, and Medical Service of the Johns Hopkins Hospital.

Chairman's address, read before the Section on Internal Medicine at the 105th Annual Meeting of the American Medical Association, Chicago, June 13, 1956.

rarely, a not very loud slightly crescendo presystolic murmur. At the base not infrequently a systolic murmur is heard over the second and third left interspaces, which may have a suggestive rubbing quality,[2] and this is increased in intensity by pressure with the bell of the stethoscope. This murmur may be related to dilatation of the pulmonary conus, which frequently is seen in fluoroscopic and x-ray examinations of these patients. Systolic blood pressure is slightly raised and diastolic pressure lowered, giving an increased pulse pressure, which accounts for the bounding pulse and visible increase in the systolic excursion of the carotid arteries while maintaining a normal mean pressure. Pulsations of the liver and even of the spleen have been observed.

These signs bespeak an overactive heart. In patients past 40 years of age or suffering from coronary artery or rheumatic heart disease, auricular fibrillation frequently ensues. A plausible theory has been advanced for the development of this and some other types of arrhythmia occurring in thyrotoxicosis. The presence of small areas of ischemia in the muscle of the auricle secondary to coronary vascular disease could induce fibrillation in a heart that is overactive from thyrotoxicosis.[3] When angina pectoris occurs in these patients, signs of thyrotoxicosis usually are less prominent or obvious than in other cases and the attacks of pain cease after the hyperthyroid state has been relieved.[4]

In the 1920's Robinson headed an already distinguished group—Burwell, Blalock, and Harrison—in exploring the problems of circulation and the physiology of cardiac output. It was found that in thyrotoxicosis the blood volume is increased, the cardiac output increased, the blood flow accelerated, and the skin capillaries dilated.[5-7] In these respects the heart of a patient with thyroid disease was similar to the heart of the patient with vitamin deficiency or beriberi, but reasons for these changes were not apparent.

Studies of Hyperthyroid and Normal Animals

In an effort to elucidate these facts, many observations have been made of the effect of thyroid extract on the circulation and on the metabolism of the myocardial cells of animals. All attempts to alter cellular activity or metabolism by exposure to thyroid extract in vitro failed completely. More conclusive information was gained through comparison of the metabolism of tissues removed from hyperthyroid and normal animals. Rohrer [8] (1924) found increased oxygen use in intact organs (liver, kidney, muscle) from white mice fed thyroid. In animals, after an injection of 1 mg. of thyroxine, Dresel,[9] using the Warburg method, found large increases in oxygen consumption of liver and moderate increases in oxygen consumption of kidney tissue. McEachern [10] made direct measurements of the oxygen consumption of isolated beating auricles from normal guinea pigs and those with thyrotoxicosis by means of a modified Barcroft-Warburg microrespirometer. In 31 experiments on normal auricles and in 15 experiments on auricles from animals with thyrotoxicosis, the latter preparations were found to have a higher rate of oxygen consumption (7 to 20%) than preparations of similar weight from normal animals. He also observed [11] that, in white rats who had received multiple injections of thyroxine, tissue respiration was increased 46% for kidney, 73% for liver, and 75% for muscle of the diaphragm.

Gordon and Heming [12] in their study with use of rat tissues gave 20 mg. of thyroxine per kilogram of body weight by injection on two successive days. After a latent period of 48 hours, liver, kidney, diaphragm, and heart muscle, in that order of magnitude, showed increases in oxygen consumption, reaching a peak on the fourth day: liver 62%, kidney 37.8%, and diaphragm 28%; but the heart muscle reached a maximum of 24% on the third day and consumption fell off rapidly on the fourth day. Tissue from brain and spleen showed no increase

in metabolism, and, of the tissues showing increased oxygen consumption, the kidney was the only one to develop an increase in respiratory quotient.

Tachycardia, once provoked in the intact animal (rabbits) by thyroid feeding or thyroxine injection,[13] persists in the isolated perfused heart and isolated perfused auricles and increases far more than normally on addition of epinephrine to the perfusate. The general picture, after a latent period of 12 to 48 hours, is one of persistent increased heart rate and increased oxygen consumption of both the beating and the quiet heart muscle, clearly demonstrating the direct effect of the thyroid hormone on the action and metabolism of the heart muscle as well as on the general body metabolism.

When one attempts to explain tachycardia in hyperthyroidism as the direct effect of thyroxine on the myocardium alone, one encounters certain difficulties. The oldest known one of these is the fact that, in cases of heart block in man, hyperthyroidism induced by feeding up to 28 grains (1.8 gm.) of extract daily fails to change the slow ventricular rate, although the basal metabolic rate becomes elevated and the auricular rate may rise from 70 to 120 beats per minute.[14] Also, a few years ago cardiac catheterization at the coronary sinus in a hyperthyroid patient yielded no evidence of increased oxygen consumption in the left ventricular heart muscle.[15] When this was repeated last year by other investigators,[16] however, the coronary blood flow in eight patients with hyperthyroidism was found significantly increased while the arteriovenous oxygen differences remained constant, thus revealing an accelerated myocardial oxygen consumption. After effective treatment with radioactive iodine (I^{131}) in these cases of hyperthyroidism, the cardiac output, cardiac work, coronary blood flow, and myocardial oxygen consumption returned to normal.

In rats made hyperthyroid with desiccated thyroid powder, Ullrick and Whitehorn[17] found respiration increased 77% in resting atrial, 22% in resting ventricular, and 33% in diaphragmatic muscle, while in skeletal and smooth muscle there was no increase. This difference in utilization of thyroid extract between auricle and ventricle may help to explain, in cases of heart block, the lack of response of the ventricle to thyroid extract, which is no longer controlled by the more sensitive auricle. Using a different technique, with sliced tissues from rats injected with one large dose of thyroxine, Barker and Klitgaard[18] obtained a quicker and larger proportional increase in oxygen utilization by left ventricular muscle than by any other tissues, while brain, spleen, and testis showed no increase.

These observations made on surviving tissue from laboratory animals rendered hyperthyroid by injecting or feeding thyroid hormone cannot be compared with any degree of confidence to the activity of similar tissues in patients suffering from toxic diffuse goiter. They do, however, fit generally the facts that are being learned about circulatory changes in hyperthyroidism. The difference of oxygen utilization between various organs, and particularly between atrial heart muscle and ventricular heart muscle, has far-reaching implications.

Blood Flow and Oxygen Consumption in Hyperthyroidism

Recent studies made by Stead and coworkers[19] in 18 hyperthyroid patients estimated blood flow and oxygen consumption of the liver or the brain or the kidney in comparison to total cardiac output and body metabolism. Measurement of the rate of removal from the blood stream by the liver of sulfobromophthalein (Bromsulphalein) by catheterization of the hepatic vein gave results that, by applying the Fick principle, indicate that the hepatic blood flow is increased very slightly in hyperthyroidism and in some cases not at all, whereas the oxygen consumption of the liver is increased disproportionately. Further studies using improved techniques, which should give more accurate measurements, may change these figures, but it seems probable that the basic facts will find confirmation.

In nine other patients with hyperthyroidism, it was found by the nitrous oxide technique that none of the cerebral metabolic functions varies significantly from the normal in this disease. Cerebral blood flow and oxygen utilization remain unchanged in hyperthyroidism,[20] although both had previously been shown to be lowered in myxedema. The renal blood flow is somewhat increased in hyperthyroidism and somewhat diminished in hypothyroidism. Blood flow to the skin is greatly increased. Cardiac output, or total blood flow, is increased proportionately much more than total body metabolism. Thus, in hyperthyroidism the over-all arteriovenous oxygen difference actually represents an average of excessive rate of oxygen withdrawal in some tissues (splanchnic), a reduced rate in others (skin and possibly muscle), and an unchanged rate in still others (brain and heart muscle).

Formerly it was believed that blood flow to an organ was increased or decreased to compensate for the changing metabolic demands of that organ. In the light of present knowledge this theory no longer is tenable. For instance, in hyperthyroidism the metabolic level in the liver is much higher than in other organs, yet the blood flow is roughly within normal limits. On the other hand, the metabolic rate in the brain is not increased nor is the blood flow altered. Peripheral blood flow is increased and is greatly out of proportion to increase in metabolism, whereas renal blood flow is moderately increased and there is evidence of only moderate increase in renal cell metabolic rate. The increase in total cardiac output is greater proportionately than the increase in total metabolic rate. One major and extremely important function thus accomplished is the provision of additional blood flow for transport of the increased body heat to the skin surface. Heat regulation depends in large measure on neurocirculatory reflexes. Thus we see that the increased blood flow in toxic diffuse goiter, which by measurement is proportionately greater than the body metabolism, provides, and provides accurately, for loss of excessive body heat. This important balance could hardly be accomplished in toxic diffuse goiter by the slowly acting direct effect of thyroid hormone on the circulation by way of the auricular heart muscle or elsewhere when the production of this hormone is clearly out of normal control.

From these observations one can assume that the increased blood flow in hyperthyroidism, which goes predominantly to the skin and possibly also to the skeletal muscles, is regulated in order to provide for heat loss through the skin. The increased oxygen requirement is satisfied, in the splanchnic organs for instance, if not necessarily in muscle, by more complete oxygen removal from the blood in passage. (This relative short supply of oxygen to the liver has been postulated as the cause of the central necrosis seen in the liver of some patients with thyrotoxicosis.[21])

Whether there is increased blood flow to the resting skeletal muscles, which in hyperthyroidism may be merely a by-product of increase to the skin, or whether, as seems more likely, such an increase serves a useful function, is not clear. Muscular weakness has long been recognized as part of the clinical picture of hyperthyroidism. Although the intimate action of thyroid hormone on cellular metabolism is not established, current concepts hold that it may act by uncoupling oxidative phosphorylation, leading to inefficient oxygen consumption and impaired use of energy sources important for contractile processes.[22] Thus it is postulated that some such metabolic defect in the myocardium may contribute significantly to the development of heart failure when it occurs in thyrotoxicosis.

Response of Heart in Hyperthyroidism

These circulatory changes all afford proof of the increased load borne by the heart in hyperthyroidism. The constant maintenance of an increased flow of blood by a heart whose muscle cell reserve energy supply may be impaired and whose rapid rate robs it of most of its usual rest period during diastole,

constitutes a strain that challenges the underlying normality of the myocardium.

Peculiarities of the cerebral blood vessels prevent such wide swings of blood flow as are common in the splanchnic and peripheral circulation. To a lesser extent the same holds true for the coronary arteries. As we have seen, however, neither of these areas can spare itself from the effects of the reduced blood flow resulting from hypothyroidism and myxedema.

In evaluating the circulatory changes seen in hyperthyroidism, we may recall certain observations on normal circulatory variations. Hamilton [23] says that "cardiac output seems to be regulated as the summation of the demands for blood by the several organs of the body, each in control, so to speak, of its own blood supply." For example, the normal cardiac output can change from a resting figure of about 6 liters per minute to a value of perhaps 15 in mild exercise, brought about mostly by an increase in rate. After hemorrhage, cardiac output may be reduced to half or less of the resting figure. Meanwhile these fivefold changes in cardiac output may be present with blood pressure changes, which are relatively small and are held in balance by alterations in peripheral resistance.

The three main forces governing circulation—cardiac output, arterial pressure, and peripheral resistance—are interdependent. When any of these is held constant, say arterial pressure, then the usual variations occurring frequently in the circulation are brought about by a balanced change of the other two, namely output and resistance. This is usually expressed by the formula C. O. = P/R.

If the rate of peripheral resistance is the pivotal factor, as Hamilton and other physiologists believe, around which blood flow (including, of course, heart rate and stroke volume) must vary while maintaining satisfactory blood pressure, then this is the area primarily involved in hyperthyroidism and/or hypermetabolism. Local demands are answered by local dilatation of the arterioles, with consequent increase in blood supply. "This," says Hamilton, "is mainly in response to local chemical influences and is dependent, to little or no degree, upon reflex adjustment of vascular tone. [It appears that this generalization may not be applicable to thyrotoxicosis.] When we become overheated, [however] hypothalamic reflexes are activated which cause cutaneous dilation and heat is dissipated. Both of these vasodilator mechanisms are prepotent, that is will hold vessels open in spite of vasoconstrictor outflow from the medulla." Because the circulatory changes taking place in hyperthyroidism are far from simple, the facts as known today are certainly subject to misrepresentation. We must remember, also, that there are elements of emotional tension that introduce nervous and hormonal stimulation of the heart as well as of the peripheral vascular system. The results of all of these direct stimuli call forth activity on the part of many reflex homeostatic mechanisms, including the arterial stretch receptors (i. e., carotid sinus).

Homeostasis, as Cannon conceived it, is achieved by methods of balance provided by innumerable physical, chemical, and biological rheostats. It is obvious that conflicts between these systems are continuous. In each equation the imbalance most threatening to survival must be given priority in the attempt to restore normality. Arterial blood pressure must be maintained to ensure satisfactory circulation. Therefore in thyrotoxicosis even if accurate control of body temperature is the important factor that initiates homeostatic changes in the circulation, these changes can occur safely only if they permit the maintenance of arterial blood pressure adequate to perfuse essential organs. It is at this point that the heart responds reflexly to maintain the balance. With these facts in mind, some of the detrimental effects of circulatory changes in thyrotoxicosis can be more readily understood.

Myxedema

In many ways the circulation in myxedema presents a mirror image of that in

toxic diffuse goiter. Results of studies are usually confused by the presence of complicating conditions such as old age, anemia, or actual coronary artery disease. The case of one young female patient (aged 21) with apparently uncomplicated myxedema from a group of five studied by Ellis and coworkers[24] with use of the venous catheter and direct Fick method, may provide the best example of the effect of thyroid deficiency on otherwise normal circulation. The alterations that were corrected later by replacement therapy were (1) increased peripheral resistance (threefold), (2) increased pulmonary resistance (twofold), (3) cardiac output lowered (nearly threefold) beyond the degree of lowered oxygen need (−20%), (4) reduced stroke output (threefold), (5) increased heart size (2 cm. in transverse diameter in the orthodiagram), (6) diminished blood volume (1000 cc.), (7) increased arteriovenous oxygen difference (more than twofold), (8) narrowed femoral artery pulse pressure but unchanged mean pressure, and (9) low voltage in the electrocardiogram. Remaining normal, in this particular case, were pulse rate, circulation time, pulmonary artery pressure (even after exercise), right auricular pressure, and venous pressure.

Here again change in total body metabolism cannot account for the large reduction in blood flow. On the other hand, the degree of increased peripheral resistance compares with that of blood flow, while mean arterial pressure remains the same. Since in this case the pulse rate remains the same, the lowered cardiac output is accomplished by lowered stroke volume. Electrocardiographic changes did not develop after one month of thyroid deprivation. Circulation time may be normal or even relatively increased through certain viscera while being reduced through the skin. By the usual methods of measurement, it has been found reduced in most cases of myxedema. Cardiac enlargement may represent weakened myocardium from thyroid deficiency or may be part of the general new circulatory balance and account, at least in part, for the reduced blood volume. The increased arteriovenous oxygen difference is produced by reduction in blood flow, which is greater than the reduction in oxygen consumption. Lowered blood flow to the skin, with vasoconstriction and increased resistance, seems to constitute the initial change in the circulation in myxedema.

Conclusions

When one reviews the facts that are currently known concerning the changes produced in the circulation of the human being by hyperthyroidism and hypothyroidism, one reaches a somewhat surprising hypothesis. Triggered by change in body temperature, produced by the increase or decrease in metabolism, the homeostatic neurocirculatory mechanism provides for change of blood flow to the skin by vasodilation or constriction. From the ensuing change in peripheral resistance, cardiac output is reflexly increased or diminished, with tachycardia and/or increase in stroke output, or the opposite, while mean arterial blood pressure is preserved in its normal range. The fact that the myocardium shares in the general metabolic effect of the thyroid hormone contributes no doubt to the maintenance of the new level of circulatory performance.

Various viscera appear to function at different metabolic levels. Their varying oxygen needs seem to be satisfied in some cases by increased blood flow and in others by increased oxygen withdrawal from a more or less constant blood supply. Different organs and tissues respond to excess of thyroid hormone with various levels of metabolic rate. This probably reflects similar degrees of varying utilization of the hormone under normal conditions. Confronted by the difficulties of adapting to imbalance of this particular hormone, the circulatory system reacts in ways that are in some cases beneficial and in others detrimental.

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Clinical Syndromes Produced by Isolated Dysfunctions of the Renal Tubule

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It is certain that the speakers to come before the Section on Experimental Medicine will present differing views concerning the hypertension problem, but it seems equally certain that none of them will dare to ignore the kidney. Until the present confusion subsides no one can say whether the chief culprit will be caught lurking in the nervous system, the adrenal cortex, the electrolyte panel, or the kidney, but it is hard to deny that renal epithelium shares the guilt.

The responsible processes are of course not yet understood, and opinion is therefore sharply divided between the "hyperrenalists" on the one hand, who believe that the kidney secretes an excessive amount of pressor and vasopathic material, and the "renoprivalists" on the other hand, who note how difficult it is to produce endocrine hypertension without first reducing kidney mass. Quite possibly both views are right, in that under circumstances not yet defined renal hypertension may be an excitatory phenomenon while under other conditions the kidney may fail to control inherent pressor tendencies.[1] In either event chemical processes within the kidney cell have clearly gone astray.

The term renal failure usually implies oliguria, azotemia, or both, but subtler and more interesting varieties exist. My comments about them will be broader than they are deep, for I can only point out here that failure of the nephron to do particular chemical jobs produces many widespread metabolic disturbances other than hypertension. Some are obviously due to enzymatic dysfunction of genetic origin, some are acquired disorders, and all are poorly understood. It seems unlikely that much more information of fundamental importance will accrue from the application of the clearance and saturation tests of renal function, which have to date been so useful; future advances will probably come about through the collaboration of careful clinicians and chemists skilled in intracellular processes.

Some of the disturbances to be described resemble endocrine diseases but are really examples of Seabright-Bantam syndrome, a concept first used by Albright and his colleagues[2] to describe situations created by failure of end-organ response rather than of hormone production. Other abnormalities are clearly due to variations in glandular function, but all too often it is impossible to decide whether alterations in cellular activity are due to intrinsic or hormonal forces. Some examples will be given.

Clinical Syndromes

Defects in Water Resorption.—Diabetes insipidus is usually due to hypovasopressinemia, the result of lesions in the anterior hypothalamus, but in a few cases the condition does not respond to substitution therapy. In some of these cases not due to organic renal disease there appears to be a sex-linked recessive defect that impairs the ability of the distal tubular segments to resorb water.[3,4] The opposite condition of hypervasopressinemia, either absolute or

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relative, has not yet been defined, and from the few available reports on cases of edema of unknown origin it is difficult to decide whether retention of sodium or of water is the primary event. In one case [5] the diuretic response to corticotropin resembled that seen in nephrosis and suggested therefore that sodium retention was the initial event; in another, however, no such response occurred.[6]

Defects in Glucose Resorption.—Renal glycosuria, a defect in the enzymatic processes that enable the proximal tubule to resorb glucose, may be on a genetic basis also.[6] Conversely, this mitochondrial mechanism may operate more efficiently in some people than in others, but factors such as diminished glomerular filtration rate and renal blood flow are more reasonable explanations for a high glucose threshold.

The Kidney and Protein Metabolism.—Since there is good reason to believe that mammalian glomerular filtrate contains about as much protein as does cerebrospinal fluid (about 10 to 30 mg. per 100 cc.), the tubules of the human kidney must normally deal with 50 to 60 gm. of protein daily (180 liters of fluid multiplied by 0.3 gm. of protein per liter). Virtually all of this is resorbed, of course, and it is probable that the transport mechanism involves both catabolic and anabolic processes. Proteinuria occurs when glomerular membrane disease increases the filtered load beyond the point of tubular saturation, as in nephrosis.[8] It may or may not be coincidence that the rate of plasma protein regeneration by the human liver approximates that of renal tubular resorption; in any event, the kidney plays an important role in regulating the concentration of circulating protein.

For years Addis [9] suspected that defects in the tubular transport mechanism influence the amount of protein in the blood and urine, and an increased rate of albumin destruction had been demonstrated in idiopathic hypoalbuminemia,[10] a curious nephrosis-like picture with no evidence of renal or hepatic disease. The same inability of the tubule to return protein to the blood stream in an osmotically useful form may also exist in persons with proteinuria, but no evidence of excessive protein destruction has yet been found in nephrosis.[11]

Aminoaciduria.—While many disorders present the kidney with more amino acids than its resorptive mechanism can accommodate, primary or renal aminoaciduria is believed to be an event of great importance in the genesis of the hepatic, brain, and renal lesions of progressive lenticular degeneration (Wilson's disease), the de Toni-Fanconi syndrome, and cystinuria.[12] Paper chromatography has recently uncovered a rather common familial tendency to the excretion of β-aminoisobutyric acid, but the meaning of this genetic abnormality is not yet apparent.[13]

Defects in Tubular Transport of Cations.—Some defects in the resorption of cations and excretion of electrolytes are given below.

Sodium and Potassium: The ability of aldosterone to increase the tubular resorption of sodium and to diminish that of potassium has been brilliantly described by Conn [14] but hypoaldosteronism has not yet been recognized except as part of the picture of generalized adrenocortical failure. Electrolyte excretion is also controlled by enzyme systems in the tubule cells, especially carbonic anhydrase, which enables the nephron to resorb sodium in exchange for hydrogen. Deficiency of this enzyme has already been suspected in a patient with hypokalemia whose tubules secreted potassium at a high rate but hydrogen in diminished amounts and whose condition was relatively refractory to treatment with acetazoleamide (Diamox).[15]

Calcium: Idiopathic hypercalciuria, responsible for a high proportion of kidney stones, apparently represents a genetic inability of the tubule to resorb calcium in proper amounts.[16] It is important to distinguish this primary type of calcium deficit from those that occur as secondary responses to such stimuli as hyperparathyroidism, immobilization of the skeleton, chronic acidosis, high calcium intake, or vitamin D poisoning.

Since normal individuals tolerate large amounts of alkali, at least for a short period of time,[17] it may be that the "milk-alkali" syndrome occurs only in the presence of a renal defect that permits excessive resorption of calcium from tubular fluid. Chronic hypercalcemia unrelated to diet has also been described in combination with hyperphosphatemia, osteosclerosis, renal insufficiency, and dwarfism, but the pathogenesis is not understood.[18]

Magnesium: Not enough is known about the tubular transport of magnesium to warrant discussion.

Defects in Tubular Transport of Anions.—Some defects in the resorption and secretion of anions is given below.

Chloride: In general the tubular transport of the chloride ion is the same as that of sodium.

Bicarbonate: Whether due to inability of the proximal convolution to resorb bicarbonate[19] or to failure of distal segments to secrete hydrogen or ammonium ions,[20] or to both, hyperchloremic acidosis exists as an isolated genetic defect.[21] It is important because of the destructive effect that prolonged negative balance has upon the skeleton and the kidneys. Serious losses of other cations, especially potassium, may also occur, but the entire process can be checked by adequate alkali therapy.

Phosphate: With the description of hypocalcemic tetany unresponsive to parathyroid hormone, Albright and colleagues[2] first introduced the Seabright-Bantam concept into clinical medicine—a very useful line of thought. It is due to the fact that the renal tubule continues to resorb phosphorus at a high rate despite adequate parathyroid function. The opposing condition, that of chronic phosphate diuresis, results in a type of rickets that is relatively resistant to vitamin D; it is a dominant trait[22] and could represent a deficiency of phosphatases and phosphorylases in the proximal tubule.

de Toni-Fanconi Syndrome.—Finally, the coexistence of multiple defects in almost any combination results in variants of the de Toni-Fanconi syndrome.[23] The classic combination of glycosuria, aminoaciduria, and phosphate diabetes involves a single recessive trait.[22]

Summary

Hypertension is due at least in part to specific defects in renal tubular function and can thus be classified among such other metabolic diseases as nephrogenic diabetes insipidus, renal glycosuria, idiopathic hypoproteinemia, primary aminoaciduria, idiopathic hypercalciuria, renal hypokalemia, chloride acidosis, pseudohypoparathyroidism, vitamin D-resistant rickets, and the de Toni-Fanconi syndrome.

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Simple Tests of Renal Function in Health and Disease

I. *A Reappraisal of Their Value in the Light of Serial Renal Biopsies*

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Although the naked eye examination of the urine was extensively practiced from the earliest historical times, the first valid clinical deduction from urine analysis was recorded in India and China some 2500 years ago.[1] In the West, Thomas Willis (1621-1675 A. D.) was the first to use urine analysis in differential diagnosis, having noted that the urine of patients with diabetes mellitus was sweet, whereas that of other patients with polyuria (diabetes insipidus) was not.[1] In the Middle Ages detailed inspection of the urine was widely used to diagnose all the ills of mankind, from pregnancy (Fig. 1) to phthisis. Ultimately this medieval and renaissance hocus-pocus was effectively quashed in 1637 A. D. by Thomas Brian's blunt broadside, quaintly entitled: "The Pisse-Prophet, or Certaine Pisse-Pot Lectures, wherein are newly discovered the old fallacies, deceit, and jugling of the Pisse-Pot science used by all those (whether Quacks and Empiricks or other methodicall Physicians) who pretend knowledge of Diseases, by the urine, in giving judgment of the same."[2]

Fig. 1.—A medieval physician diagnosing pregnancy by inspection of the urine.

Misinterpretation of modern tests of renal function can be almost as fallacious as medieval urine inspection. They do not provide, as yet, a short-cut to diagnosis and management of renal disease, which must rest on the examination and close observation of the patient. The indications, usefulness, and limitations of simple tests of

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renal function and of urine analysis have been dealt with in a most authoritative manner by Ham and his colleagues.[3] Their analytic discussions of laboratory examinations as related to the urinary system were based on clinical, laboratory, and autopsy experience gathered by the profession prior to 1950, in an era when Henry Christian wrote,[4] "It is not possible to diagnose accurately during life, the anatomic changes that are found in the kidney after death." Since 1950, percutaneous renal biopsy has been developed into a safe and effective technique for study of the kidney in health and disease.[5,6] During the past five years, the clinical value of renal biopsy in the diagnosis, prognosis, and management of renal disorders has been placed on a sound footing.[7,8] Single renal biopsies provide tissue for exact histologic diagnosis in diffuse affections of the kidney, and serial biopsies capture and illuminate the dynamic processes of injury, reaction, and repair in the organ. Comparisons and correlations of urine analysis, tests of renal functions, and "living" histology can now be made for the first time and will allow us to make a critical reevaluation of these laboratory procedures in the study and care of the patient. In this paper we will present correlations between function and structure which must of necessity be preliminary in nature. Renal biopsies have been done for only a few years, and we have taken barely 500 to date. Many thousands of biopsies must be harvested and many years must pass before sufficient data have been collected to define exactly the relationship between structure and function in disease of the kidney. Nonetheless, some pertinent data have been obtained, and these will be presented together with observations on 33 patients ill with systemic lupus erythematosus (SLE) and lupus nephritis. The details of this study are being published elsewhere.[9] It is possible to report observations on lupus nephritis at this time, as it is a specific form of glomerulonephritis in which the renal lesions progress at a more rapid rate than usually occurs in other forms of Bright's disease.

Methods of Study

Thirty-three patients with SLE were studied on the medical services of three hospitals. The criteria used for the diagnosis in these patients have been reported elsewhere.[9,10] In all patients renal function was assessed by the following tests.

1. *Urinalysis.*—In every case fresh early morning specimens were examined shortly after collection. Clean voided specimens from male patients and catheter specimens from female patients were examined. A portion of each specimen was submitted for bacteriological culture. Fluids were restricted for 12 hours before the collection of the specimens for urinalysis.

The specific gravity of the urine was tested at room temperature with a standardized urinometer. The protein was estimated semiquantitatively, using the sulfosalicylic acid method. Estimations of 24-hour protein excretion were made on most patients by the phosphotungstic acid method.* In a few the Esbach method was used. In addition the pH was measured with nitrazine paper; glucose with Clinitest tablets, and acetone, with Acetest tablets. Fifteen milliliters of urine was centrifuged for five minutes at 2000 rpm and the concentrated sediment resuspended by agitating in a few drops of urine. It was then examined microscopically with low- and high-power magnification. Polarized light was used for the identification of anisotropic lipids.

2. Specific Gravity.—The specific gravity of the urine was measured following a period of 14 hours of fluid deprivation. Four specimens of urine were collected, and the maximum specific gravity was recorded.

3. *Urea Clearances.*—Urea clearances were determined for a single two-hour period. An average urine flow of at least 2 ml. per minute was attained in most patients. This was achieved by giving the patient six to eight glasses of water to drink during the first 90 minutes of the test (1200-1500 ml.). The results were expressed as a percentage of average normal renal function (75 ml/minute=100% when the urine flow was greater than 2 ml/minute; 54 ml/minute=100% when the urine flow was less than 2 ml/minute).

4. *P.S.P. Excretion.*—Six milligrams of phenolsulfonphthalein (P. S. P.) was injected intravenously after a water load had been given. The bladder was emptied completely (by catheterization of the female patients) 15 minutes later, and the excretion of P. S. P. was measured on a Coleman Junior spectrophotometer.

These three tests were always done under the same conditions by one of the authors. Serial

* References to the methods used in this paper are given elsewhere.[9]

observations were made at the same time of day and under the same conditions of hydration.

5. *Biochemical Examination of the Blood.*—In all cases the following biochemical examinations of the blood were done: blood creatinine by the method of Peters; blood urea nitrogen (B. U .N.) by the Conway method; blood nonprotein nitrogen (N. P. N.) by the method described by Koch and McMeekin; serum proteins by the Cohn method. The total serum cholesterol was determined by a modification of the method of Bloor.

Renal Biopsy and Pathology.—The biopsy and histological techniques are described elsewhere.[6] The histological sections were analyzed in minute detail. Twenty elements from glomeruli, tubules, interstitial tissue, and vessels were assessed individually in each biopsy. The degree of damage to each element was graded on a semiquantitative scale from 0 to 4+. From this minute analysis an estimate of total glomerular damage, of total tubular damage, and of over-all kidney damage was derived. Full details of this analysis will be published elsewhere.[8]

Results

Over a period of three years 33 patients with SLE were studied. A total of 65 histological studies was made, 57 by renal biopsy and 8 at autopsy. Function studies were made in all cases at the time of biopsy or shortly before death. In eight patients there was no histologic evidence of renal disease; one had nephrosclerosis. In the other 24 patients there was histologic evidence of lupus nephritis. Serial studies were made in 24 patients; three or more studies were made in 7.

(1) *Urine Sediment.*—The relationship of urine sediment to renal structure and the progress of the disease is shown in Tables 1 and 2. From these tables it is evident that the earliest changes in the kidney can develop without abnormality in the urine. In Table 2 it can be seen that a good correlation exists between the number and variety of elements in the urine and renal damage.

(2) *Proteinuria.*—The amount of protein in the urine was plotted on scattergrams against the degree of tubular damage, glomerular basement membrane thickening, and glomerular hypercellularity (Figs. 2, 3, and 4). No correlation was found with glomerular hypercellularity, but inspection of the charts indicates that there is a good positive correlation between the amount of protein in the urine and the degree of structural damage to the glomerular basement membrane and to tubular damage. †

TABLE 1.—*A Comparison of Urinalyses and Histologic Findings in the Kidneys of Patients Ill with SLE*

Renal Histology	Normal Urinalyses	Abnormal Urinalyses
No evidence of lupus nephritis	12	3*
Lupus nephritis	7†	40

*Pyelonephritis in one and nephrosclerosis in another.
†In these seven tissues only minimal changes were seen.

(3) *Nitrogenous Substances in the Blood.*—Blood creatinine was measured on 58 occasions (Fig. 5). This was within normal limits (less than 1.4 mg/100 ml.) in 16 cases with normal kidneys, in 16 of 17 cases in which the renal damage was estimated at 1+, and in 7 of 10 in which the damage was 2+. It was greater than 3 mg/100 ml. in all nine cases with severest renal damage (4+).

The blood urea nitrogen was measured 58 times (Fig. 6). This was within normal limits (less than 14 mg/100 ml.) in 15 of 16 patients with normal renal histology, in 10 of 17 in whom the renal damage was esti-

† Dr. H. C. Batson gave advice regarding evaluation of the data.

TABLE 2.—*A Comparison of the Urinary Sediment and Histologic Findings in the Kidneys of Patients Ill with Systemic Lupus Erythematosus*

Urinary Sediment	Histologic Findings			
	Normal	Glomerulitis	Proliferative and Membranous Glomerulonephritis	Subacute or Chronic Glomerulonephritis
Normal	12	7	0	0
RBC + WBC +	3	4	2	0
WBC + Casts +	2	2	5	0
RBC + Casts +	0	2	2	1
Casts +++ WBC + RBC +	0	0	7	13

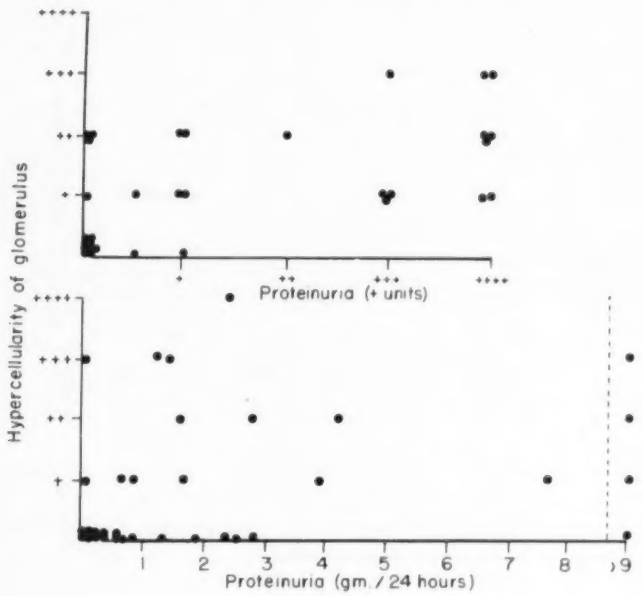

Fig. 2.—Scattergram showing poor correlation between glomerular hypercellularity and proteinuria.

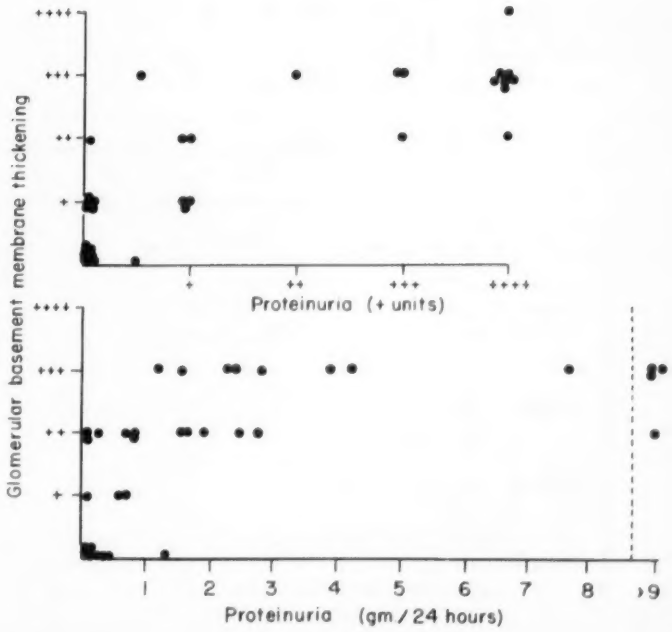

Fig. 3.—Scattergram showing good correlation between glomerular basement membrane thickening and proteinuria.

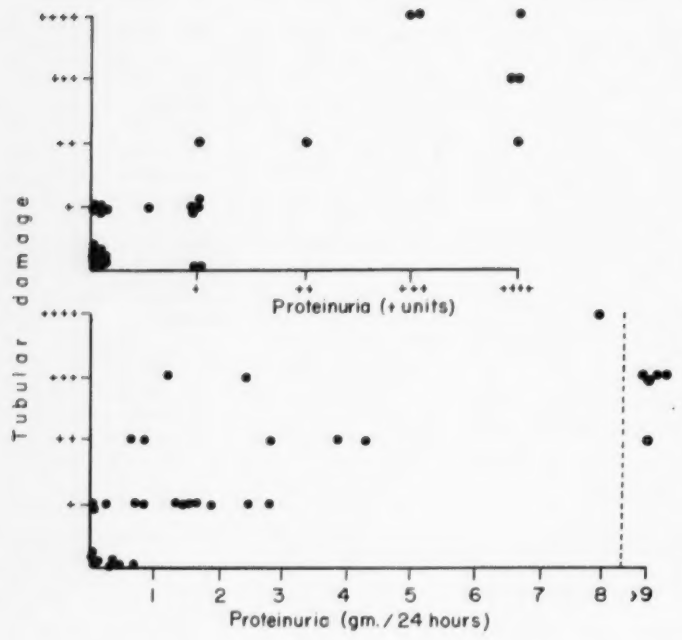

Fig. 4.—Scattergram showing good correlation between tubular damage and proteinuria.

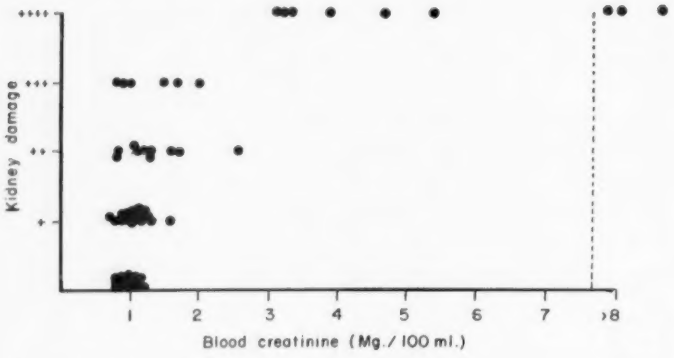

Fig. 5.—Scattergram showing the relationship between over-all kidney damage and serum creatinine.

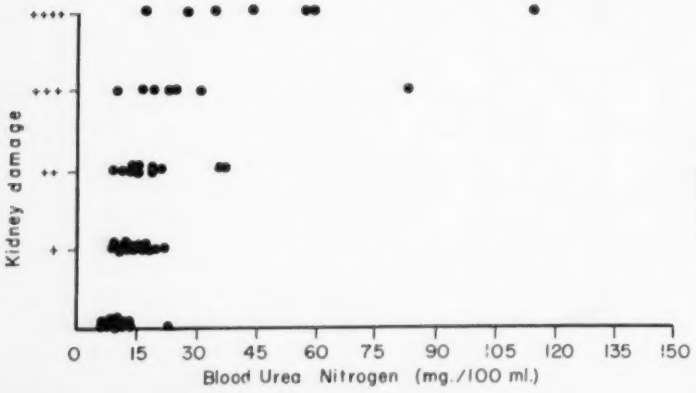

Fig. 6.—Scattergram showing the relationship between over-all kidney damage and blood urea nitrogen.

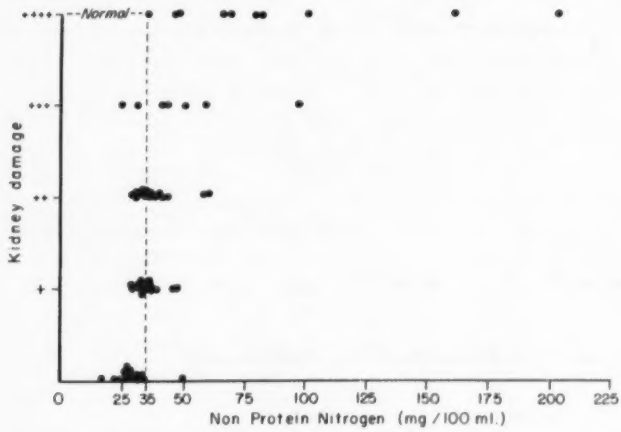

Fig. 7.—Scattergram showing the relationship between over-all kidney damage and serum nonprotein nitrogen.

mated as 1+, in 4 of 11 with 2+, and once with 3+ renal damage. B. U. N. levels of more than 30 mg/100 ml. were encountered twice in patients with 2+ damage and in seven patients in whom the lesion was more advanced.

The blood nonprotein nitrogen was measured in 63 patients (Fig. 7). The level was normal (less than 35 mg/100 ml.) in 15 of 16 patients with normal kidneys, in 8 of 14 cases in whom the renal damage was estimated at 1+, and in 7 of 15 in whom it was 2+. The N. P. N. was normal in only 2 of 18 cases in whom the renal damage was estimated as 3+ or 4+.

(4) *Specific Gravity Concentration.*—Specific gravity concentration tests were done in 43 instances. The results are shown in Figure 8. The maximum urine concentration was 1.022 or greater in 21 of 26 cases with normal kidneys or 1+ kidney damage and in 4 of 7 cases with 2+ damage. In all 10 cases in which the renal damage was 3+ or 4+ the maximum urine concentration was less than 1.020, and it was below 1.015 in 5 of 6 cases with 4+ damage. No significant differences were observed when the maximum urine concentration was plotted either against grades of glomerular damage or against grades of tubular damage.

(5) *Urea Clearances.*—Urea clearances were measured in 51 instances, and the results are shown in Figure 9. It is seen that there is a close correlation between the degree of renal damage and the urea clearance expressed as a percentage of average normal renal function. Values of less than 50% were not found until there was 2+ damage and were observed in 12 of 13 cases with more advanced lesions. Again no significant differences were observed when the

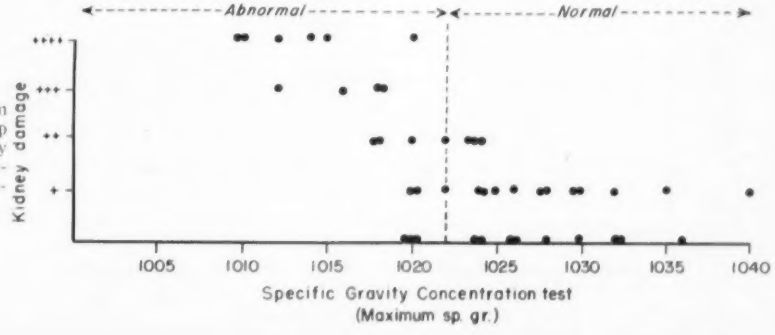

Fig. 8.—Scattergram showing the relationship between over-all kidney damage and urine specific gravity concentration.

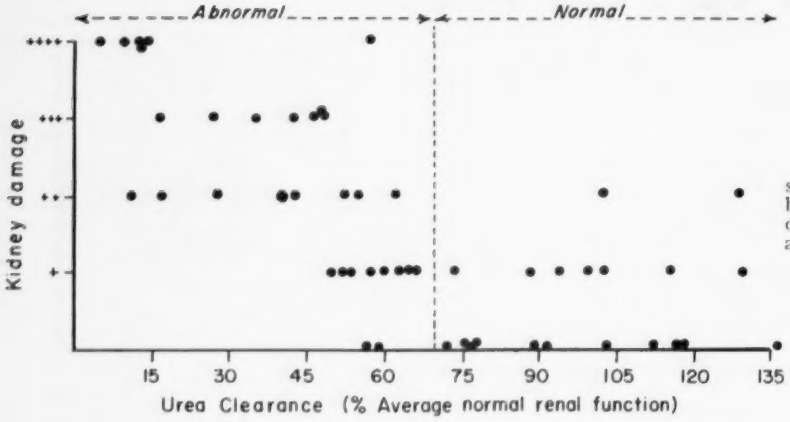

Fig. 9.—Scattergram showing the relationship between over-all kidney damage and urea clearance.

urea clearance was plotted against glomerular damage or against tubular damage.

(6) *Phenolsulfonphthalein Excretion.*—Phenolsulfonphthalein excretion tests were made on 59 occasions (Fig. 10). Twenty-five per cent or more of the injected dose was excreted within 15 minutes in 26 of 34 cases with normal kidneys or 1+ renal damage. The excretion was below 25% in 9 of 12 cases with 2+ damage and in 4 of 7 cases with 3+ damage, and was less than 15% in all seven cases with 4+ damage. A similar distribution of results was obtained when P. S. P. excretion was plotted against glomerular damage or tubular damage.

Comment

It is axiomatic that the basic macroscopic, chemical, and microscopic examination of the urine should be considered as part of the physical examination of the patient. We believe, as Addis did,[11] that these simple studies of the urine should be done by the physician in charge of the patient, because the symptoms and signs of active renal disease, other than abnormalities in the urine, may often be absent or quite obscure.

The results of the study of renal function and histology in lupus nephritis confirm what many have suspected for diffuse diseases of the kidney in man. When a diffuse

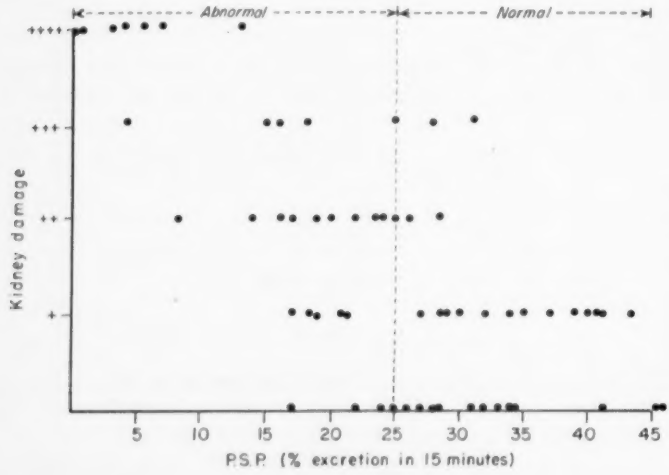

Fig. 10.—Scattergram showing the relationship between the over-all kidney damage and the 15-minute P. S. P. excretion.

kidney disease first develops, the ordinary clinical and laboratory methods may not reveal that anything is wrong. When the ordinary clinical methods of study indicate that there is an abnormality, they do not indicate exactly what is wrong nor how much renal tissue is involved by the disease process unless and until the kidney is severely damaged.

Proteinuria.—There was poor correlation of proteinuria with glomerular hypercellularity, but a good correlation was observed both with the degree of glomerular basement membrane thickening and with the degree of tubular damage. This could mean either that proteinuria was produced by damage to both these renal elements, or that it was produced by damage to one—the change in the other structural element being coincidentally related to the same underlying disease process. Finally, the proteinuria may have come from some other source which was not studied, such as the renal pelvic lymphatics—which might have been damaged or disturbed *pari passu* with the progressive damage to glomeruli and tubules. This problem of interpretation applies to all positive correlations of the type of data presented. Our data, however, do indicate that the constant finding of gross proteinuria in a patient with S. L. E. correlates well with glomerular basement membrane and tubular damage and is of serious prognostic significance. However, in patients with the nephrotic syndrome the proteinuria usually decreases as the edema clears, either in spontaneous improvement, as a result of treatment, or with progression of the renal disease.

Urinary Sediment.—Correlations between urinary sediment and histologic findings are shown in Table 2. It is apparent that the number of casts increases with increasing kidney damage, as is well known. But what is not well demonstrated is that early in the development of lupus nephritis, leukocytes may appear in the urine in large numbers and even in clumps. This may suggest, incorrectly, a diagnosis of pyelonephritis. Staining the urinary sediment by the method of Sternheimer and Malbin [12] makes interpretation of the formed elements considerably easier. The Sternheimer, or "glitter," cell is a swollen polymorphonuclear leukocyte with pale blue-staining, ill-defined nuclei; its cytoplasm contains grey granules which show Brownian movement at times. These cells probably arise from within the kidney and have been considered typical for pyelonephritis. We have also observed them in urinary sediment from a patient with severe lupus nephritis in whom there was no histologic or bacteriologic evidence of infection of the kidney. We now examine the urinary sediment both unstained and stained by Sternheimer's method. This is necessary, as the Sternheimer stain masks certain features of the urinary sediment, such as optically active fat. The presence of fat in the urine indicates deposition of fat within the tubular cells and is seen in urine from patients with diabetic nephropathy and all forms of the nephrotic syndrome.

It has been said that the urinary sediment is the renal biopsy. Our observations indicate that this is not true for the exact diagnosis of the underlying disease process. Nevertheless, it frequently gives a good indication of the activity of the disease process as shown in Table 2. Krupp described the "telescoped" urinary sediment and considered it to be diagnostic of lupus nephritis.[13] Others have disagreed with this view, and we have found "telescoped" urinary sediments from patients in whom there was no clinical or renal biopsy evidence of lupus nephritis. In one condition, however, the sediment is truly a renal biopsy—when tumor cells from the kidney are demonstrated in the urine by the Papanicolaou staining technique.[14]

Azotemia.—From Figures 5, 6, and 7 it is seen that some correlations can be made between the levels of serum creatinine, B. U. N., and N. P. N. and renal damage estimated histologically. All three parameters gave good indication of gross renal damage. However, in many instances the levels were not greatly above normal in the presence

of mild and moderate degrees of kidney damage. This was particularly true of the serum creatinine, which was raised above 1.4 mg/100 ml. in only four cases (11%) with slight to moderate damage (1+ to 2+) and in only three of six cases with 3+ damage. By contrast the levels of B. U. N. and N. P. N. were raised slightly above normal in 43% and 41% of cases with slight to moderate renal damage. At these levels of damage to the kidney the B. U. N. and N. P. N. were perhaps more sensitive indicators of histologic change than was the creatinine. However, it will be recalled that compared to creatinine the B. U. N. and N. P. N. are more subject to variation due to extrarenal factors, such as dehydration and electrolyte imbalance.

In one patient the blood creatinine level was 2.6 mg/100 ml. despite the fact that the histologic damage was not gross. She was ill with lupus nephritis and the nephrotic syndrome. We have observed that the levels of blood creatinine, B. U. N., and N. P. N. have been raised in the presence of comparatively mild histologic changes in patients with the nephrotic syndrome due to other causes. We may speculate as to whether this azotemia is due to the associated renal interstitial edema or tubular damage. When some of these nephrotic patients had a diuresis, the levels of creatinine, B. U. N., and N. P. N. returned to normal; study of a second biopsy at this time revealed that the interstitial renal edema had disappeared, and in most cases the tubules appeared healthier.[15]

Thus it is seen that the levels of serum creatinine, B. U. N. and N. P. N. are insensitive indicators of underlying renal damage, being raised only when that damage is severe. By contrast, in patients with the nephrotic syndrome, azotemia may be present whatever the pathology and whatever the extent of the renal damage and may decrease or disappear after diuresis. In the interpretation of these tests, extrarenal factors, such as diet, dehydration, depletion of sodium, a sudden fall in blood pressure, or free blood in the gastrointestinal tract which may cause azotemia, must be taken into account.

Specific Gravity Concentration.—Many years ago Volhard recognized that measurement of nitrogenous substances in the blood was an insensitive index of early renal damage. This led him to develop the specific gravity concentration test by means of which he sought to obtain information about the functional reserve of the kidney.[16] The test has the virtue of simplicity and is usually interpreted as being a test of tubular function. But Bradford[17] and Hayman,[18] among others, have shown in animals that subtotal nephrectomy results in isosthenuria, and Platt[19] has stressed that the test can also reflect the number of functioning nephrons in the diseased kidney, each nephron carrying a high osmotic load from the glomeruli and producing an osmotic diuresis. Our data support this view because impairment of concentrating power of the kidney correlated equally well with glomerular damage, tubular damage, and over-all kidney damage. Recent studies have shown that the specific gravity concentration test may show considerable impairment of function even when orthodox histology reveals no abnormality. We have studied two cases of "kaliopenic nephropathy"[20] who were unable to concentrate their urine above 1.012 and in whom the other tests of renal function were impaired. Their kidneys were histologically normal except for slight degenerative changes in the tubules. In these patients the test was probably a reflection of impaired tubular function. This provides a good illustration of the inadequacy of present-day histologic methods in the study of the renal tubules.

Urea Clearance Test.—The concept of renal clearance tests is an artificial one, as they estimate the hypothetical volume of blood cleared of an excretory product per minute by the kidney. In routine practice it is difficult to collect accurately timed urine samples. This may introduce a highly significant error into the procedure even when

the urine is collected by catheterization. The risk of infection following instrumentation of the urethra is considerable.

Clearance studies are worthless if the urine flow is below 20 ml. per hour; when urine flow is between 20 and 119 ml. per hour, the urea clearance is calculated by Van Slyke's square root formula—which is an abstraction. To avoid using this formula, a urine flow of at least 120 ml. per hour should be obtained whenever possible. In clinical practice and even in a metabolic ward this cannot always be achieved. It is for this reason that our data on urea clearance have been expressed in terms of average normal renal function as proposed by Van Slyke.[21] In spite of all these objections, the urea clearance tests (Fig. 9) gave a valuable and reproducible estimate of the general excretory function of the kidney, as shown by its relationship to over-all kidney damage and to the results of the P. S. P. excretion and specific gravity concentration tests (Fig. 8 and 10).

Phenolsulfonphthalein Excretion. — The dye is said to be excreted only by the tubules, and its rate of release into the urine is believed to reflect their integrity. This may be true for healthy persons. In lupus nephritis P. S. P. excretion was shown to be correlated with over-all kidney damage as well as with tubular or glomerular damage. This may be due to a number of causes. For example, in severe renal damage blood flow within the kidney is markedly distorted and may compromise tubular function. As with the specific gravity concentration test, the diminution of P. S. P. excretion may reflect the decrease in functioning nephrons. In either case the P. S. P. excretion test is abnormal because of over-all kidney damage. In certain types of nephrotic syndrome with severe tubular damage and normal glomeruli, the excretion of P. S. P. may be in the high normal range.[15]

It is evident from Figures 8, 9, and 10 that the results of the tests are distributed among a wide range of values for the normal and at each degree of renal damage. This is a common biological phenomenon and accounts for the fact that there was a considerable overlapping of results in each of the tests. Obviously such overlapping impairs the value of any single test when applied to the individual patient. Failure to standardize environmental conditions while doing the tests may further impair their clinical usefulness. In the second part of this paper Drs. Sargent and Johnson have indicated that many alterations can be provoked in renal function of healthy men by nutritional imbalance, caloric deficit, dehydration, physical work, and extremes of temperature. Frequently the deviations from normal were so great as to be reminiscent of the findings in pathological states. The observations strongly support the view that it is highly desirable to study the patient under conditions where diet, water intake, work, and temperature are carefully controlled. If this cannot be done, it is essential that the patient's immediate past history with respect to these variables be determined and taken into account in evaluating the results of tests of renal function.[22]

The Use of a Battery of Renal Function Tests

In patients with lupus nephritis we have shown that abnormalities in each of the function tests under discussion gave information about the structural damage to the kidney as a whole. They gave no indication of localization of the disease process to the glomerulus or tubule. This may be because lupus nephritis, like most diffuse diseases of the kidney, affects the nephron as a whole. In these circumstances it might seem reasonable to select the most sensitive single test and to rely on that test alone for a quantitative estimate of kidney damage. Table 3 shows that this is not possible, as in 15 patients only one of the three tests was abnormal, and there was no correlation between the test which was abnormal and the nature of the histologic damage. Therefore, in the presence of smaller degrees of

TABLE 3.—*Showing Number of Abnormal Tests of Renal Function as Compared with Histological Changes in the Kidney*

Renal Damage	No. Cases*	All Tests Normal	1 Test Abnormal				2 Tests Abnormal			3 Tests Abnormal
			Urea Clearance	S.G. Conc.	P.S.P.	Total	Urea Clear. P.S.P.	S.G. Conc. P.S.P.	Total	
0	14	8	2	2	1	5	1	0	1	0
+	13	5	3	1	2	6	1	0	1	1
++	9	0	2	0	2	4	1	1	2	3
+++	6	0	0	0	0	0	1	2	3	3
++++	6	0	0	0	0	0	0	0	0	6

*Only cases in which all three tests were made are included in this Table.

renal damage it is quite clear that a battery of the three tests—specific gravity concentration, urea clearance, and P. S. P. excretion—gave more accurate information about the underlying kidney damage than did any single test.

A further example of the value of the three tests is shown in Figure 11, which depicts serial studies in a patient with lupus nephritis, by means of renal biopsies and tests of renal function. This indicates that the tests are of value in observing the progression of the disease but that none of the tests help in making a diagnosis of lupus nephritis. This diagnosis can only be inferred from the clinical findings, and it can be made with certainty in the living patient only through renal biopsy and only when the typical histologic picture is found.

These limitations of present-day simple tests of renal function in the study of lupus nephritis probably apply to all forms of diffuse renal disease. Correlations between the histologic changes in renal biopsies and the more complex discrete tests of renal function will take a long time to collect,

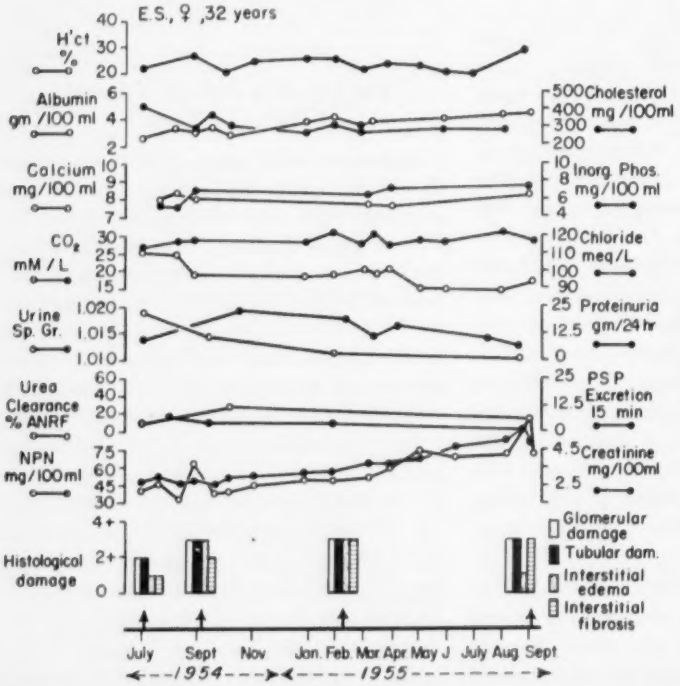

Fig. 11.—Histologic abnormalities (renal biopsies) and laboratory data in patient ill with systemic lupus erythematosus and lupus nephritis.

but some data to hand would seem to indicate that these important physiologic tests are of little value in diagnosis and not efficient in prognosticating the course of disease. Newer tests of kidney function, such as studies of the relationship between urine and serum osmolarity while the kidney is under stress from dietary and osmolar loading, may be of greater value.[22]

The observation that urine analyses and kidney function tests may be perfectly normal in the face of definite and sometimes extensive renal histologic changes is unsettling. It tends to confirm the disturbing conviction that at times it is well-nigh impossible to detect, let alone diagnose, by simple clinical methods, early disease of the organ. In this regard in 1948 Addis wrote

> Let us consider what happens in the doctor's office, or the out-patient department, when it is reported that the "routine" examination shows that the urine has a "two plus albumin." In a large proportion of such cases the most searching history and the most exhaustive physical examination fail to reveal any abnormality we can link with the proteinuria. What are we to do, then? Even when we find hypertension, edema, anemia, or arteriosclerosis, the relation between these signs and the renal lesion responsible for the appearance of the protein in the urine remains a matter of speculation. It is a question to be decided on grounds of statistical probability, on what pathologists tell us about the frequency of association of various diseases of the kidney, and those external symptoms we observe. It is not determined by anything we can see for ourselves and really know about the patient.

Is there a way out of this seeming impasse? We believe there will be. To date, approximately 500 percutaneous renal biopsies have been done by us. There have been no serious complications, and morbidity was slight. The results indicate that renal biopsy is a most valuable tool in the diagnosis and management of diseases involving the kidney, and it has been of singular assistance in assessing prognosis.[7] The fullest information for control of the patient can be obtained by correlating the histologic data with the history, physical findings, urinalysis, and a battery of renal function tests, in the manner shown in this study.

Summary

Correlations between renal histology obtained by percutaneous renal biopsies, urine analyses, nitrogenous substances in the blood, and three simple tests of renal function (urea clearance, P. S. P. excretion, and specific gravity concentration tests) were illustrated by a study of 24 patients with lupus nephritis and of 9 patients with SLE and normal kidneys. Histologic analyses assessed over-all kidney damage for 57 biopsies and 8 autopsies, and damage to glomerular structures, tubules, interstitium, and vessels was graded semiquantitatively from 0 to 4+.

On 13 occasions normal urine analyses were found when there was histologic damage to the kidneys. Good correlations were found between the degree of renal damage and the three simple tests of renal function. When several studies were done on the same patient, serial function studies reflected serial histologic changes. With mild renal changes a battery of tests was more useful in detecting abnormalities than single tests. The clinical value of percutaneous renal biopsy in diagnosis, management, and prognosis of renal disease is evident when compared with simple tests of renal function.

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DISCUSSION

DR. ELLIOT V. NEWMAN, Nashville, Tenn.: I believe studies like that of Dr. Kark and his colleagues are adding a new dimension to the understanding of renal disease. So much of our knowledge of renal disease from the standpoint of pathology has been retrospective. Now we can have a fresh contemporary view of the anatomical process. I would not be surprised if this new look at renal pathology causes us some confusion in our previous concepts before it causes clarification.

It seems to me that there are additional exciting possibilities for study of these biopsies. I refer to chemical and enzymological examination of the tissue. It may be possible to administer dyes, blocking agents, and tagged materials prior to biopsy. In this way, the sample of tissue may be used for investigation of biochemical and

physiological as well as anatomical changes in disease.

Our methods of determining functional changes in renal disease in the past have had great limitations. It is, after all, quite indirect to attempt to ascertain the exact site and extent of disease within the renal parenchyma by examination of urine from the bladder. The physiologist has used great ingenuity in interpreting the type of change in the nephron from the characteristics of the mixed bladder urine. But, a direct look at the nephron is now possible.

In the past 15 years, we have witnessed the development of very nice renal function methods and their application to the study of renal disease. I am referring to the methods such as inulin and PAH (*p*-aminohippuric acid) clearances, and the PAH and glucose T_m (maximum tubular excretory or secretory capacities). Discrete functions of the nephron can be determined by this type of physiological dissection. These methods, however, are based on net results on mixed urine from the whole kidney.

Thus, the technique of renal biopsy not only adds a new dimension of time to the picture of renal disease, but it offers us the possibility of direct correlation of physiological with microscopic pathology. Dr. Kark's studies point the way.

Since Dr. Kark has used the usual practical clinical renal function tests for correlation with the anatomical picture, I thought it might be worth while to make a few criticisms of these tests which we use in practice, as I believe many of us have made mistakes in applying these tests clinically. I refer specifically to three tests: the P. S. P. excretion test, the concentration test, and the microscopic examination of urine sediment.

It may seem superfluous to mention obvious technical details, but it is worth while emphasizing that the P. S. P. excretion test requires the accurate administration intravenously of exactly 1 cc. (6 mg.) of dye—no more or less. This can be done with reasonable accuracy only with a syringe of the long-scale variety (tuberculin or insulin type).

There is a custom in some quarters of requiring the patient to empty the bladder before injecting the P. S. P. dye. This would not be a serious error if this procedure were merely useless, but in addition it may make it more difficult for the patient to void subsequently at the required time of the first collection. After all, one usually must dilute the specimen with water to make the determination. Dilution with the urine already in the bladder is not wrong.

Another custom of highly questionable value is the collection of samples in fractions of the total two-hour period following the injection of P. S. P. A variable part of the first fifteen minutes is taken up by the passage of the dye through the circulatory system to the kidney, then through the kidney, and finally down the calyceal—pelvic—ureteral tract. This total time from vein to bladder is usually called the "appearance time" or "delay time." This "delay" is caused mostly by the volume of urine in the urinary tract and is dependent on the rate of urine flow. The appearance of greater amounts of dye in a later than in a previous period of time always means pooling in the system. This occurs in hydronephrosis where the volume in the system is large, or it occurs most often when there is variable emptying of the bladder. These collection errors affect the accuracy of the total 2-hour collection the least and affect the first 15 minutes the most. The longer the period of collection and the larger the urine flow, the more accurate the test. Aside from the evidence of inaccurate collection or pooling which fractional collections may reveal, I know of no significance of the fractional results which is not revealed simply by the total two-hour collection excretion.

The amount of dye excreted by the kidneys depends primarily on two factors: first, the number of functioning tubules; secondly, the flow of blood to the tubules. If the test is done with the patient up and around and under physical stress, the result may be low because of lowered renal blood flow. This is more striking in cases of cardiac failure. A higher value will often be obtained by keeping the patient quiet and supine.

The concentration test is a very valuable index of physiological integrity of the kidney. The ability of the kidney to elaborate urine of high specific gravity can only be revealed if conditions exist which require the kidney to make this response. We have all had the somewhat annoying experience of finding in a random specimen of urine a higher specific gravity than was found during a planned test period. There are three conditions which must coincide to produce a high specific gravity (assuming no glycosuria or proteinuria). There must be first a stimulus to retain water, secondly a stimulus to excrete salt, and, thirdly, a sufficient excretion of urea. I have observed many times attempts to carry out a concentration test on patients who are eating prescribed low-salt diets. One can hardly blame the kidney for not concentrating the urine if the ratio of water to solids in the diet is high. The kidney would be quite abnormal if, under these circumstances, the urine were not diluted. The stimulus to retain water is mediated by the posterior pituitary gland, which is subject to many influences, including psychological and hormonal.

Lastly, Dr. Kark's studies prompt me to make

a few remarks about microscopic examination of the urinary sediment. In the past, the closest approximation to a renal biopsy in the patient with renal disease has been the urinary sediment. Now we have the opportunity to determine the significance of the sediment more accurately in terms of microscopic renal pathology. I believe it is fair to say that the art and technique of examination and interpretation of urinary sediment has been gradually neglected in this era of progressively increasing use of "routine laboratories" for the "routine urinalysis." Perhaps this trend is more evident in hospitals than it is in office practice, where the urine can be examined freshly and immediately alongside of the patient. The passage of the urine specimen through several messengers and a storage period in an ice box before being examined by a technician along with 50 other specimens is not a mechanism which is conducive to the most accurate interpretation.

I think we all welcome a fresh approach to the problems of renal pathology. The studies reported here by Dr. Kark and his colleagues should create added significance and accuracy in the methods in common use for assessing renal disease and documenting the changes with time and treatment.

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Simple Tests of Renal Function in Health and Disease

II. Simple Tests of Renal Function: Healthy Subjects

FREDERICK SARGENT II, M.D., and ROBERT E. JOHNSON, M.D., Urbana, Ill.

In conditions of nutritional imbalance or exposure to such environmental stresses as work, heat, and cold, renal functional changes resembling pathological alterations may be observed in healthy young male subjects. In this paper we shall discuss physiological changes which must be accounted for in evaluating the results of routine urinalysis and quantitative tests, such as urea clearance, creatinine clearance, and osmotic clearance.

Qualitative Findings

Reaction.—Diets which are acid in ash or ketogenic often drive the urinary pH down as low as 5.5 and the titrable acidity as high as 50 mEq/day. By contrast, diets of alkaline ash often drive the urinary pH as high as 8.0. In such specimens the titrable acidity is zero.

Glycosuria.—Glycosuria in healthy young men is extremely rare. In approximately 1600 tests of 211 male subjects exposed to environmental extremes of heat and cold and also exposed to extreme nutritional stress, such as starvation for two weeks, we obtained positive tests only five times, and none of these was over 1+. Clinitest tablets were used in all these analyses. In short, a strongly positive sugar reaction can be a very significant finding.

Ketonuria (Rothera Reaction).—Unlike glycosuria, ketonuria of significant degree is easily produced in healthy subjects by nutritional imbalance and exposure to cold and hard work. Exposure to extreme cold regardless of diet will produce a ketonuria, whereas life in hot climates seems not to predispose to ketonuria (Sargent and Consolazio, 1951). Another general condition which produces ketonuria in healthy men is hard work followed by a period of rest without food (Sargent and Consolazio, 1951). Caloric deficits when extreme enough will regularly evoke ketonuria. Among 40 subjects who starved for periods ranging from 7 to 14 days, reactions of +4 were almost invariable. Decreasing the caloric deficit moderates the ketonuria except when the nutrient intake is predominantly from fat. When caloric deficits of the order of 1000 Cal/man/day were imposed on 24 subjects who were receiving 2000 Cal/day of pure carbohydrate, no ketonuria was observed in two weeks. On the other hand, when the caloric deficit and intake were the same as before, a diet providing 70% of the Calories from fat and 30% from protein invariably caused marked ketonuria. In view of the extreme rarity of glycosuria in normal young persons, a finding of glycosuria together with ketonuria must be regarded as definitely abnormal.

Albuminuria (Sulfosalicylic Acid Test).—Experience with 1600 tests conducted on urine from over 200 male subjects under standard conditions of rest and recumbency has led to the conclusion that albuminuria may be found after moderate exercise, such as marching, and during exposure to moderate cold. Caloric deficit and varying distributions of Calories among protein, carbohydrate, and fat are unrelated to the appearance of albuminuria. However, dur-

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From the Department of Physiology, University of Illinois. Research was conducted in the University Health Service Research Unit. Associate Professor (Dr. Sargent), Head (Dr. Johnson), Department of Physiology, University of Illinois, College of Liberal Arts and Sciences.

ing rehabilitation after such abnormal regimens albuminurias of +1 are not uncommon. Very rarely reactions of +3 may be observed under such circumstances. Albuminuria which persists from week to week is extremely rare. We have seen it only in one subject.

Morphology

When an accurately timed urinary specimen is collected under standard conditions of rest and recumbency and the frequency of formed elements is assessed according to the concepts of Addis (1925), it can be shown that microscopic hematuria and cylindruria may occur in healthy male subjects. Among the major stresses which we have studied, dietary imbalance is far more conducive to cylindruria and hematuria than are exposure to environmental heat and cold, physical work amounting to 290 Cal/hour, or chronic dehydration of two week's duration. With great regularity starvation for two weeks or a dietary regimen consisting of pure carbohydrate will be accompanied by a urinary excretion of 250,000 casts per hour and 50,000 red blood cells per hour. Although the great majority of the casts are hyaline casts, a few granular types may be seen. On occasion unbalanced diets high in fat will also provoke microscopic hematuria and cylindruria. Balanced diets, even when fed so as to produce caloric deficits

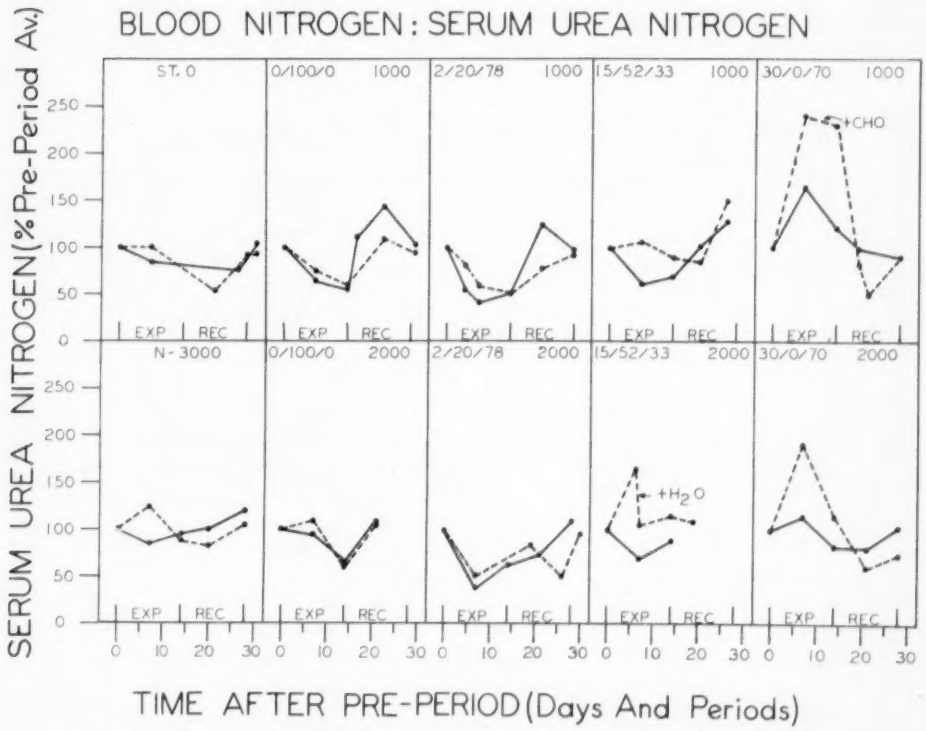

Fig. 1.—Serum urea nitrogen and diet. Continuous lines, water ad libitum in all periods. Dashed lines, 900 ml. of water/day in experimental (EXP) periods. Numbers in upper portion of blocks refer to percentage distribution of Calories between protein, carbohydrate, and fat, respectively, and daily caloric intake in the experimental periods; ST.O indicates starvation; N-3000, five-in-one ration at 3000 Cal/day; REC, recovery period when subjects ate five-in-one ration ad libitum; +CHO and +H_2O refer to alterations in nutrient regimen necessitated by clinical condition of subjects. Mean preperiod serum urea N, 9.1-15.3 mg/100 ml., for 12 university students.

of 2000 Cal/day, very rarely produce such changes in urinary sediment. Although the physiological mechanism of this phenomenon is not evident, the cylindruria and hematuria regularly disappear during rehabilitation from such nutrient regimens.

When the white blood cells and epithelial cells in the urine are studied quantitatively, the predominant findings are (1) tremendous individual variability and (2) lack of correlation with any of the dietary and environmental stresses studied. After an hour of moderate work, the excretion of these cells tends to become smaller.

Quantitative Chemical Changes

In three years of nutritional investigation on 211 healthy male subjects we have systematically studied renal function by currently popular clinical tests. Striking functional changes, in some cases approaching pathological values, may be produced by nutritional imbalances or deficiencies.

Serum Urea, Nonprotein Nitrogen, and Creatinine.—A combination of chronic dehydration and a diet which contains over 12 gm. of nitrogen per day invariably raises the concentration of urea, nonprotein nitrogen, and creatinine in the blood. Values of 40-50 mg/100 ml. of urea nitrogen are common (Fig. 1). These high values may be prevented or ameliorated by an adequate water intake or a low protein diet.

Creatinine and Urea Clearance.—Creatinine clearance diminishes during caloric deficiencies independently of the percentage of Calories from protein, carbohydrate, and fat (Fig. 2). In starvation values as low as 40% of the normal for that subject may be observed. For any given nutrient regimen

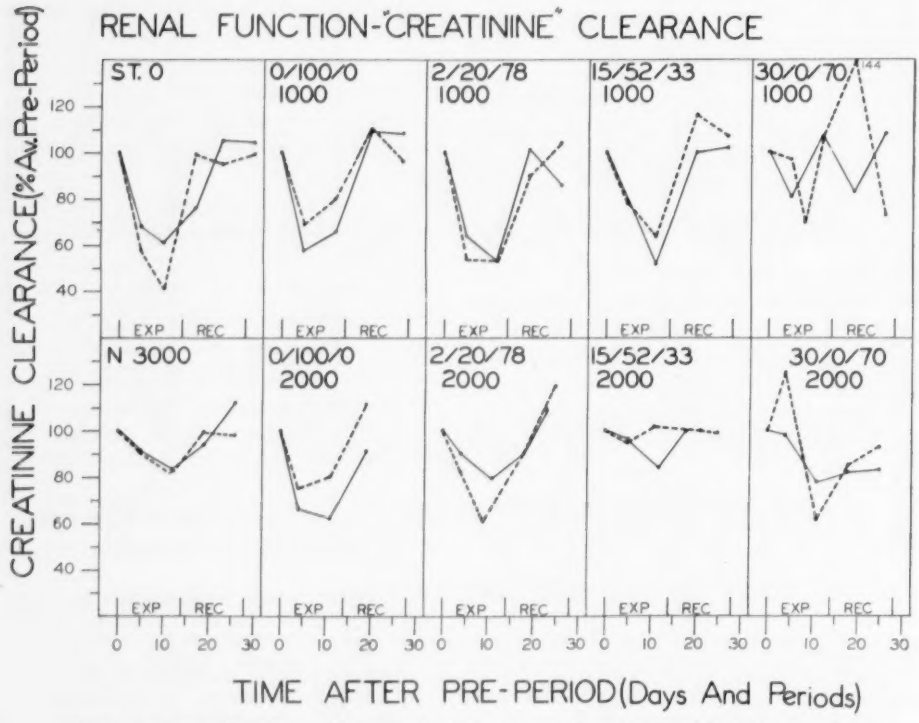

Fig. 2.—Renal function. "Creatinine" clearance as determined with 24-hour urinary specimens. Mean preperiod creatinine clearance, 147-170 ml/minute for 12 university students. Other symbols same as in Figure 1.

a greater diminution will be found with intakes of 1000 Cal/day than with 2000 Cal/day. In contrast to its effect on serum nitrogenous values, chronic dehydration does not significantly alter the creatinine clearance. When the nitrogen intake is high, the values for creatinine clearance tend to be somewhat erratic. This variability has been reported by several other workers (Addis et al., 1951; Camara et al., 1951; Schoch and Camara, 1952). Changes in urea clearance comparable to those shown in Figure 2 have been reported by other investigators, notably McCance and Widdowson (1937), during periods of combined sodium depletion, caloric deficit, and moderate protein intake.

Osmotic Clearance.—If the concept of clearance is applied to electrolytes and total osmotically active substances, gross variations in diet will produce large alterations in the numerical values of the clearances. For instance, in a group of 16 male subjects after two weeks of a diet consisting of pure carbohydrate the mean value of osmotic clearance had diminished to approximately 20% of normal, and the values for sodium and chloride clearances were zero.

Conclusions

In order to evaluate properly any test of renal function—whether by routine urinalysis or by quantitative clinical function tests—it is highly desirable that the patient be studied under standard conditions in which diet, environment, and activity are closely controlled. If such control is not possible, then the patient's previous history with respect to these variables must be taken into consideration in the differential diagnosis of abnormal findings.

Since submission of this article, a full and detailed account of the findings summarized here has been published (Sargent, F., II, and Johnson, R. E.: The Effects of Diet on Renal Function in Healthy Men, *Am. J. Clin. Nutrition* 4:466-481 [Sept.-Oct.] 1956).

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Treatment of Hyperthyroidism with Individually Calculated Doses of I^{131}

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With the Assistance of Lucille E. Shoop, R.N., Los Angeles

Radioactive iodine has been used for the treatment of hyperthyroidism for 14 years. During this time no entirely satisfactory method of dosimetry has been developed. Some institutions employ "shotgun" doses, ranging from 3 to 9 mc., depending on the severity of the disease or size of the thyroid gland,[1-4] while others attempt to administer 100 to 250μc for each gram of estimated thyroid weight.[5-8] A number of groups have taken other factors into account, namely, the number of roentgen equivalents to be administered to the hyperthyroid gland, the maximum per cent uptake of a tracer dose of I^{131}, and the "effective" or observable half-life, as well as the thyroid gland size and weight.[9-11]

Allen and Goodwin,[12] in 1952, reported a method of calculating the weight of the thyroid gland based on point by point plot of the thyroid area following a tracer dose of I^{131}. Goodwin, Cassen, and Bauer greatly simplified this method by the use of the scintigram.[13]

It is the purpose of this paper to report the results of treatment of a series of thyrotoxic patients with a therapeutic dose of I^{131} based on the following factors:

1. The number of roentgen equivalents to be delivered to each gram of thyroid tissue.
2. The maximum per cent thyroid uptake of a tracer dose of I^{131}.
3. The "effective" half-life of this tracer dose.
4. The weight of the thyroid gland calculated from the scintigram.

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From the Radioisotope Service (Chief [Dr. Bauer]; Asst. Chief [Dr. Blahd], and Nurse [Mrs. Shoop]), Wadsworth General Hospital, Veterans Administration Center, and the Department of Medicine (Associate Clinical Professor of Medicine [Dr. Bauer] and Assistant Clinical Professor of Medicine [Dr. Blahd]), University of California School of Medicine at Los Angeles.

Patient Material

Age and Sex.—In this series there were 106 patients, 90 men and 16 women. The ages of the men ranged from 25 to 78 years, with a mean of 44.8 years, and of the women, from 26 to 67 years, with a mean of 44.6 years.

Thyroid Gland Morphology.—One hundred four of the patients had diffuse glands; two had toxic nodules.*

Previous Therapy for Hyperthyroidism.—Of the 106 patients, 8 had undergone partial thyroidectomy previously and presented themselves with a recurrence of their disease.

Seventeen patients had been treated with thiourea drugs, methimazole, or strong iodine (Lugol's) solution before being referred for I^{131} therapy. In these patients either medical therapy had been unsuccessful in effecting or maintaining a clinical remission or surgical therapy had been refused after symptoms were controlled. Medication was discontinued in these patients for about four weeks before diagnostic tests (I^{131} tracer test, protein-bound iodine, and serum cholesterol) were done.

Preexisting Complications.—Sixteen patients had exophthalmus. Twenty patients had cardiovascular disease, attributable either solely to hyperthyroidism (thyrocardiacs) with later complete reversal of their heart disease as evidenced by clinical and electrocardiographic criteria, or to heart disease due to other causes aggravated by hyperthyroidism. Two patients had thyrotoxic

* It is the practice in this hospital to treat toxic nodular goiter surgically. The two patients treated with radioactive iodine had severe cardiovascular complications which made them poor surgical risks.

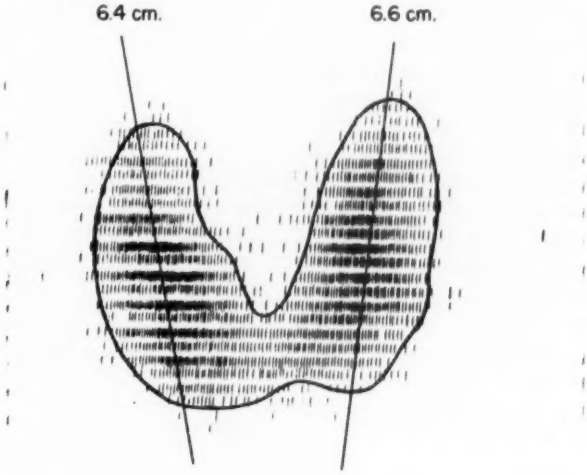
myopathy, and two patients had myasthenia gravis. Two patients had gynecomastia at the time of their initial examination.

Procedure

The patients were admitted to the wards of Wadsworth General Hospital. The clinical diagnosis of hyperthyroidism was substantiated by the protein-bound iodine determination, basal metabolic rate, serum cholesterol, and radioactive iodine uptake.[14] All patients were then presented to the Hospital Radioisotope Committee for confirmation of the diagnosis and therapeutic recommendations. This series is composed of those patients for whom I^{131} therapy was recommended.

The tracer test was performed as follows: The patient was given a capsule of about $2\mu c$ of I^{131} after breakfast. Uptake by the thyroid gland at a distance of 10 cm. was measured at 6- and 24-hour intervals. This technique makes possible the use of very small tracer doses and minimizes the contribution of extraneous counts from extrathyroid tissue. The normal values obtained in this laboratory are as follows: 7% to 23% in 6 hours (with a mean of 14%) and 14% to 35% in 24 hours (with a mean of 23%).

The effective half-life or observable disappearance of the tracer from the thyroid gland was measured by plotting the net counts (thyroid counts less thigh counts [the "body background"]) on semilogarithmic paper against time for three to five days. In euthyroid persons the effective half-life is seven to eight days; in hyperthyroids it is usually, but not invariably, shorter, indicating rapid release from the gland.



Planimeter reading cm^2 x average length cm x factor = wt. in gms.

30.3 x 6.5 x .321 = 63.2 grams

$$\frac{\text{Roentgen equivalents} \times \text{T-1/2 Physical } I^{131} \times \text{thyroid gland weight}}{\text{Roentgen equivalents 1 uc } I^{131} \times \text{T-1/2 effective} \times \text{\% uptake}} = 6.2 \text{ mc. } I^{131}$$

$$\frac{7000 \times 8 \times 63.2}{160 \times 4.3 \times .83} = 6.2 \text{ mc. } I^{131}$$

Fig. 1.—Calculation of the weight of the thyroid gland and the therapeutic dose of I^{131} in patients with hyperthyroidism.

The weight of the thyroid gland was obtained from the scintigram which was done after the estimation of the effective half-life, usually on the fifth day after the administration of the tracer dose. A dose based on the maximum per cent uptake of the tracer dose and sufficient to concentrate 60μc of I^{131} in the thyroid gland was administered orally. The gland was scanned 24 hours later with the scintiscanner. The outline of the silhouette of the gland was drawn. The area was then measured with a planimeter, multiplied by the average length of both lobes and a factor to account for the volume (Fig. 1). This factor in our laboratory has been found to be 0.321.[13,15] In instances when the isthmus was very small or absent, the weights of the thyroid lobes were individually calculated and summed.

The formula for the determination of thyroid weight is as follows:

Area (sq. cm.) × length (cm.) × 0.321 = gm.

Dosimetry.—It is generally agreed that from 6000 to 15,000 equivalent roentgens (e. r.) are required for I^{131} therapy of hyperthyroidism in diffuse glands, whereas more is needed for toxic nodular goiter. In this series of 106 patients we attempted to deliver an arbitrary dose of 7000 e. r.

The formula used to determine the therapeutic dose, based on Quimby's formula,[16] was as follows:

$$\frac{7000 \text{ e.r.} \times 8 \times \text{thyroid weight (gm.)}}{160 \text{ e.r.} \times \text{ef.h-l.} \times \text{max.\% uptake}} = \mu c\ I^{131}$$

where 8 is the physical half-life of I^{131}; ef.h-l. is the effective half-life in days, and max.% uptake is the maximum percentage uptake of the tracer dose.

It is estimated that one microcurie of I^{131} emits 160 e. r. during its complete physical decay. Of these 160 e. r. there are 144 e. r. due to β-radiation and approximately 16 e. r. due to γ-radiation.

The patients were followed at monthly intervals on an outpatient basis and their clinical status checked in conjunction with determinations of serum protein-bound iodine, serum cholesterol, and I^{131} tracer studies. Tracer studies were done two to three months after the therapeutic doses had been administered, since residual radioactivity in the patient's thyroid gland made it impractical to do so sooner.

Additional therapy doses were given three months after the first dose if the clinical status so warranted. Several patients continued to have laboratory tests indicative of hyperthyroidism, but it was decided to treat the patient rather than the test. These patients will be discussed below.

Radioiodine Studies Before Therapy.—The maximum per cent uptake of a tracer dose at six hours was 14% to 99%, with a mean of 53.7%, and 23% to 94% at 24 hours, with a mean of 60%.†

The effective half-life (T-½) in 103 patients is shown in Table 1. In three patients effective half-life determinations could not be done. In the calculation of these therapy doses, the effective half-life was estimated to be five days.

TABLE 1.—*The Effective Half-Life (T½) in 103 Patients*

T-½, Days	No. Patients	Per Cent
3	6	5.8
4	23	27.2
5	31	25.2
6	26	25.2
7	12	11.7
8	5	4.9

The weight of the thyroid gland as calculated from the scintigram is shown in Table 2.

TABLE 2.—*Weight of the Thyroid Gland as Calculated from the Scintigram*

Weight, Gm.	No. Patients	Per Cent
Under 25	16	15.4
25–50	48	46.1
50–75	24	23.1
Over 75	16	15.4

The highest initial gland weight was 151 gm.; the lowest, 15 gm., and the average weight, 48 gm.

In two patients, scintigrams could not be done. Their gland weight was estimated by palpation.

† Two of the patients with diffuse glands had maximum uptakes of less than 35% in 24 hours in the presence of clinical hyperthyroidism.

A 51-year-old Caucasian woman had an uptake of 29% in 6 hours and 32% in 24 hours; an ef-

(Footnote continued on following page)

Results

Table 3 shows the number of I^{131} doses given the 106 patients. Total number of doses, 170. Of the two patients who required more than three therapy doses, one had malignant exophthalmos and the other had arteriosclerotic heart disease with toxic nodular goiter. The therapy doses were calculated as outlined above.

TABLE 3.—*Number of Doses of I^{131} Required to Induce a Euthyroid State*

No. Doses	No. Patients	Per Cent
1	60	56.6
2 or more	46	43.4
2	34	32.1
3	10	9.4
5	1	0.9
7	1	0.9

The average total dose required to effect clinical remission was 8.21 mc. The highest total amount for one patient was 39.9 mc. in five doses. The highest single dose was 20 mc., and the lowest single dose was 1.7 mc.

Of the 106 patients treated, 100 (94.3%) were clinically euthyroid within three to five months after the institution of therapy. Only one patient had a recurrence of hyperthyroidism which occurred after a three-year period of euthyroidism.

Clinical improvement was noticeable three to six weeks following the therapy dose, usually manifested by decreased nervousness and weight gain. The patients who developed permanent hypothyroidism had a more rapid clinical response, usually beginning two weeks after therapy.

Radioiodine uptake studies following I^{131} therapy showed a return to normal of the 24-hour values within six months. The initial rate of uptake as measured by the 6-hour test was invariably more rapid than normal even in the presence of a normal 24-hour value.[17] Fourteen patients showed this pattern of abnormally high 6-hour and normal 24-hour values at the time of preparation of this paper in the presence of a clinically euthyroid state and normal PBI. In 15 patients who required additional therapy doses the thyroid uptake was higher than that obtained prior to the first therapy dose. It was lower in 25 patients and unchanged in 4.

The effective half-life in the patients requiring additional therapy doses became shorter in 17 patients, longer in 14, and remained the same in 12. In three of the patients it could not be done.

The weight of the thyroid gland in the patients who had to be re-treated was found to be greater in 14 patients (30%), less in 28 patients (60%), and remained the same in 2 patients. In two patients the scintigram could not be obtained.

In those patients who required a third dose, the gland became larger between the second and third doses in 5, smaller in 10, and remained the same in one.

Complications

Permanent Hypothyroidism After I^{131} Treatment.—Of the 106 patients, 6 (5.7%) developed hypothyroidism, both clinically and by laboratory evidence. Their hypothyroidism is readily controlled by small doses of desiccated thyroid. Stimulation by thyroid-stimulating hormone failed to effect improvement in three cases. It is of interest that all of these patients had received only one therapy dose of I^{131}. Analysis of their clinical status and laboratory findings (I^{131} thyroid uptake test, effective half-life, and gland weight), however, failed to reveal any

fective half-life of 3 days (normal 7-8 days); and a thyroid gland which was calculated to weigh 22 gm. The PBI was 8.3γ per 100 cc. After a therapy dose of 7.9 mc. of I^{131} she became euthyroid.

A 26-year-old Negro man with severe exophthalmos and weight loss had uptake values of 14% in 6 hours and 25% in 24 hours; an effective half-life of 4 days; and a thyroid gland which was calculated to weigh 21 gm. His PBI was 5.8γ per 100 cc., the serum cholesterol 105 mg. per 100 cc., and the basal metabolic rate +32%. In view of the clinical picture he received a therapy dose of 6.0 mc. I^{131} and became euthyroid. Subsequent tests revealed a continuing short effective half-life. The exophthalmos did not regress, but chemosis and suffusion disappeared.

unusual or distinguishing features (Table 4).

Temporary Hypothyroidism. — Seven of the 106 patients (6.6%) showed signs and symptoms of hypothyroidism 6 to 10 weeks after therapy (Fig. 2). The most striking symptoms were muscle aches of the shoulder girdle and "Charley horses" of the calf muscles. This was readily controlled by reassurance and stimulants, such as amphetamine, and mephenesin (Tolserol) for muscular relaxation. Thyroid medication was withheld so as to permit the patient's thyroid to regain its function.

Radiation Thyroiditis.—None of the patients complained of soreness of the neck.

Exophthalmos.—One patient who did not have exophthalmos before therapy (exophthalmometer reading 16 mm.) developed bilateral exophthalmos three months following I^{131} therapy (20 mm.). It did not require treatment. Of the 16 patients who presented that complication at the time of I^{131} therapy, the exophthalmos improved in 3 and did not change in the other 13 patients. In none of them did it become worse.

Increase of Symptoms.—None of the patients had an increase of the symptoms of hyperthyroidism, nor did any patient develop thyroid "crisis."

Gynecomastia and Acne.[18]—Thirteen patients (12.3%) developed transient gynecomastia and/or acne 6 to 10 weeks following therapy with I^{131}.

Pretibial Myxedema.—One patient developed pretibial myxedema three months

TABLE 4.—*Patients Who Developed Permanent Hypothyroidism Following One Therapeutic Dose of* I^{131}

Patient No.	Age	Sex	Race	Preexisting Complications	Pretreatment	Max. % Uptake of Tracer Dose	T-½, Days	Gland Wt., Gm.	Therapy Dose, Mc.
1	59	M	W	Angina pectoris	Propylthiouracil	90	5	76	5.4
2	46	M	W	....	....	70	4	60	8.0
3	32	M	W	....	....	60	4½	52	9.2
4	30	M	N	....	....	74	6	73	8.3
5	45	M	W	Malignant exophthalmos	Propylthiouracil; strong iodine solution; Cortisone	60	5	44	5.1
6	35	M	W	....	....	54	6	63	6.7

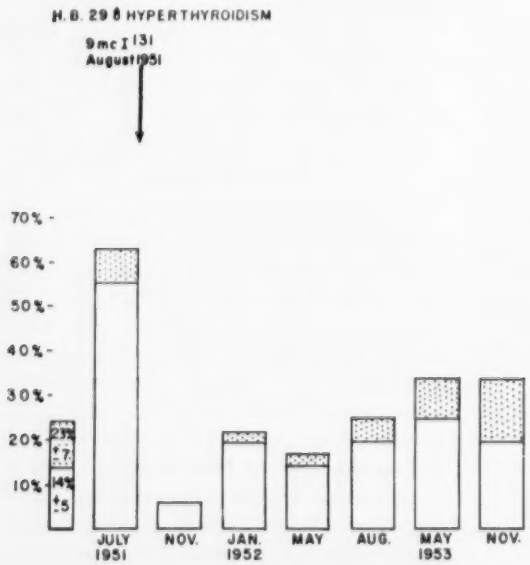


Fig. 2.—Thyroid uptake values in a hyperthyroid patient treated with I^{131}. The column on the left shows the normal values and standard deviation for the 6-hour (blank) and the 24-hour (stippled) uptake. In October and November of 1951 the patient had temporary hypothyroidism, which disappeared spontaneously. Thyroid medication was withheld.

following therapy. It disappeared spontaneously. Three months later this patient was euthyroid.

Myasthenia Gravis.—Two patients, one man and one woman, had myasthenia gravis and associated hyperthyroidism. In both, I^{131} therapy aggravated the myasthenia severely. The woman's requirement for neostigmine increased to astronomical levels, and she died of her disease in a respirator. The man's requirements also increased, but he is well controlled at this time.

Effect on Cardiovascular Complications.—Most patients with preexisting heart disease, either due to thyrotoxicosis alone or thyrotoxicosis superimposed or other types of heart disease, became much easier to control. Auricular fibrillation either reverted spontaneously to normal sinus rhythm or was easily converted by digitalis and quinidine, whereas this type of medication had failed during the height of their thyroid toxicity. One patient who had a sinus tachycardia of 140/minute developed auricular flutter and then auricular fibrillation in the second week after I^{131} therapy.

Factors Influencing Requirement for More Than One Dose of I^{131}

The severity of the disease was a factor influencing the requirement for more than one therapy dose, as is generally recognized. The very toxic patients and those with cardiovascular complications or myopathy required more doses than the mildly or moderately toxic patients.

Patients with large thyroid glands did not require more therapy doses than those with normal-size glands (Table 5).

Pretreatment.—Of the 17 patients who had received iodides or antithyroid medication, such as propylthiouracil and methimazole, prior to I^{131} therapy, 7 were made euthyroid with one dose of I^{131} and 10 required a second dose. This is a much higher incidence of additional dose requirement than in the entire series. These patients were not particularly sicker than the patients who had not received pretreatment. They had not responded well to antithyroid medication or had refused thyroidectomy when they had become euthyroid.

No correlation could be found between the maximum per cent uptake of the original tracer dose and the failure of the first therapy dose to effect a remission, nor could a correlation be found between the effective half-life and the requirement for more than one dose of I^{131} (Tables 6 and 7). This is in contrast to the results of Schmidt and Nadelhaft,[19] who found that patients with a rapid effective half-life (shorter than four

TABLE 5.—*The Weight of the Thyroid Gland of 104 Patients with Hyperthyroidism, as Calculated From the Scintigram, and Their Requirement for More Than One Therapy Dose of I^{131} to Effect Remission*

Gland Wt., Gm.	No. Patients	No. Patients Requiring 2 or More Therapy Doses
0–20	7	5
20–40	40	14
40–60	29	12
60–80	17	8
80–100	5	2
100–120	1	1
120–140	2	0
140–160	3	2

TABLE 6.—*Results of Thyroid Uptake Tests in 105 Patients with Hyperthyroidism Before I^{131} Therapy* *

Maximum % Uptake	No. Patients	No. Patients Requiring 2 or More Therapy Doses
25–35	2	0
35–45	5	1
45–55	22	9
55–65	36	14
65–75	25	12
75–85	9	7
85–100	6	2

*One patient in the series of 106 patients received a therapeutic dose of 10 mc. I^{131} on admission because of impending thyroid storm before tracer studies could be done.

TABLE 7.—*Effective Half-Lives and Requirement for More Than One Therapy Dose to Effect Remission in 103 Patients*

T-½, Days	No. Patients	No. Patients Requiring 2 or More Therapy Doses
3	6	2
4	23	11
5	31	12
6	26	13
7	12	4
8	5	2

and one-half days) required fewer doses than those with a longer one.

The two patients with toxic nodules required two therapy doses, respectively.

Eighteen patients became clinically euthyroid, yet their laboratory tests continued to be in the hyperthyroid range. This phenomenon has recently been discussed in great detail [20] and the explanation offered that there may be low hormonal iodine stores in the thyroid gland with or without a reduced serum iodide level. Whether these patients will have a clinical recurrence of their disease remains to be seen.

Strong Iodine Solution and Antithyroid Drugs.—Four patients (3.8%) with severe disease received strong iodine solution for several weeks beginning two to three days following I^{131} therapy. The clinical improvement expected did not materialize, and three of the four patients required additional doses of I^{131}. No patient in this series received propylthiouracil or methimazole.

Comment

The data presented indicate that by taking into account the behavior of the toxic thyroid gland with respect to the I^{131} uptake, the effective T-½ of the tracer dose, and the weight of the gland, as calculated from the scintigram, more accurate dosimetry can be established for therapy with radioiodine. The low incidence (5%) of overtreated patients (permanent hypothyroidism) speaks for the validity of the method presented above.

The factors influencing the failure of a single therapy dose and the requirement for more than one dose seem to be marked toxicity, cardiovascular and neuromuscular complications, and addition of strong iodine solution following administration of the therapy dose.

The reason for overtreatment of the six patients in this series could not be established. It is of interest that all had received only one therapy dose.

Therapy of hyperthyroidism and coexisting myasthenia gravis resulted in marked aggravation of myasthenia. This is not in accord with the results obtained by Millikan and Haines,[21] who feel that associated hyperthyroidism should be treated, since in their experience the myasthenia improves in most patients.

Addition of strong iodine solution following I^{131} therapy in four very toxic patients resulted in failure in three.

The two patients with toxic nodules required amounts of I^{131} comparable to patients with diffuse glands to induce clinical remission (4 mc. and 8 mc.). However, it is usually agreed that toxic nodular goiter requires more I^{131} than diffuse glands.

Summary

The results of radioiodine therapy, using an individually calculated dose of I^{131}, in a series of 106 patients with hyperthyroidism are presented.

The therapeutic dose of I^{131} was based on the roentgen equivalents to be delivered to the gland, the maximum per cent uptake by the thyroid of a tracer dose, the effective or observable half-life of the tracer dose, and the weight of the thyroid gland as calculated from the scintigram.

Following this method of dosimetry, 100 (94%) of the 106 patients became clinically euthyroid. Six became permanently hypothyroid, all following only one therapy dose of I^{131}. Fifty-six per cent of the patients required one therapy dose to become euthyroid; thirty-two per cent, two doses; nine per cent, three doses, and two patients five and seven doses, respectively.

The effects of radioiodine therapy on the clinical signs and symptoms as well as on the laboratory findings, using individually calculated doses, are reported.

The factors influencing the requirement for more than one therapy dose are discussed.

Drs. Herbert C. Allen Jr. and William E. Goodwin participated in the treatment of the first few patients in this series.

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Paroxysmal Nocturnal Hemoglobinuria

Atypical Manifestations Suggesting an Immunologic Disease

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hemolytic disease of insidious onset and chronic course, characterized by an intracorpuscular erythrocytic defect rendering the cells unusually susceptible to hemolysis in vitro and probably in vivo upon slight acidification of the plasma. The constant feature of the disease is hemosiderinuria, rather than hemoglobinuria [1]; in some cases hemoglobinuria may occur rarely or not at all.[2-5] Although an excellent account of this syndrome was provided by Strübing, in 1882,[6] only 38 cases had been recorded by 1937.[7] Crosby's classic monograph in 1953 analyzed the clinical and laboratory features of 162 collected cases.[8] Since then, many typical cases have been readily recognized by their clinical features, with subsequent laboratory confirmation by the Ham acid-hemolysis test,[9] and 18 additional cases have been reported.[10,23]

The atypical clinical and serologic features of the following three cases rendered diagnosis difficult and merit mention. Two of these cases presented with immunologic abnormalities, the possible significance of which will be discussed below.

Report of Cases

CASE 1.—*PNH with positive Coombs test*

A 34-year-old housewife entered the New England Center Hospital on July 25, 1954, with complaints of fatigue and jaundice of three months' duration. During hospitalization elsewhere for "hepatitis," a moderate anemia had been discovered. Vitamins, iron, and "liver shots" had failed to alleviate her symptoms. She had noted no change in stool color, but dark urine was noted during the three months prior to admission. The first morning urine specimen was invariably darker than normal; the color would gradually clear on successive voidings during the day. Abdominal pain had not been noted. Past history and review of systems were unremarkable.

Physical examination on admission showed moderate pallor, slight icterus, and hepatosplenomegaly, both organs being palpable 2 cm. below their respectivce margins. Admission laboratory data, including a positive direct Coombs (antiglobulin) test[24] (Table 1), were thought to indicate an autoimmune hemolytic anemia; later, the finding of an usually dark brown urine and brown plasma led to further investigations. These confirmed the findings of a positive direct Coombs (antiglobulin) test and in addition demonstrated methemalbuminemia, hemoglobinuria, hemosiderinuria, and elevated plasma hemoglobin values (75-220 mg. per 100 cc.). Both the Ham[9] and Crosby tests[25,26] were positive, indicating the diagnosis of paroxysmal nocturnal hemoglobinuria with a possible concomitant autoimmune process. Red cell survival time studies employing Ashby differential agglutination and radiochromate methods demonstrated normal survival of infused compatible cells and marked decrease in life span of autologous cells.

The patient was placed on cortisone therapy, 100 mg. daily, and transfused with washed erythrocytes. The direct Coombs test remained positive for three months, then gradually became negative. However, since no change occurred in the severity of the anemia, the steroid was subsequently discontinued. The patient has since been followed, and during this time the hemoglobin has ranged from 4.7 to 10.6 gm. per 100 cc., with corresponding variations in reticulocytes (46% to 12%). Washed red cell transfusions were administered without incident on three occasions when the hemoglobin had fallen below 7 gm. per 100 cc.

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From the Blood Research Laboratory, a unit of the Ziskind Laboratories, of the New England Center Hospital, and the Department of Medicine, Tufts University School of Medicine.

TABLE 1.—*Admission Laboratory Data*

	Case 1	Case 2	Case 3
VPRC, /100cc.	27	28	34
Hgb., gm/100 cc.	8.1	7.6	9.6
RBC, 10^6/cu. mm.	2.51	2.73	3.42
MCV	107.5	100.2	99.5
MCH	32.2	27.8	28.1
MCHC	30.0	27.2	28.2
Reticulocytes, %	13.6	Accurate count prevented by agglutination at room temperature	5.7
Platelets, 10^3/cu. mm.	470		478
Wbc, 10^3/cu. mm.	10.2	7.2	11.5
Polymorphonuclear cells, %	49	81	51
Lymphocytes, %	47	16	22
Mononuclear cells, %	6	2	14
Eosinophiles, %	1	1	1
Basophiles, %	1	0	2
Metamyelcytes, %	0	1	6
Myelocytes, %	0	0	4
NRBC/100 nucleated cells	0	0	2
Rbc morphology 0–4+			
Polychromatophilia	3	4	2
Anisocytosis	3	2	2
Poikilocytosis	1	1	1
Hypochromia	1	2	0
Macrocytosis	3	1	1
Microcytosis	1	1	1
Spherocytosis	1	0	0
Ovalocytosis	0	1	2
"Tear drops"	Rare	Occ.	2
Direct Coombs test	Pos.	Neg.	Neg.
Osmotic fragility	0.60–.30, 50%	68–0.38, 50% at 0.54	
Bilirubin, mg./100 cc.			
Direct	0.5	0.1	0.2
Indirect	3.0	0.5	0.8
Cryoglobulin	Neg.	Neg.	Neg.
Plasma hemoglobin, mg./100 cc.	75–220	130	180
Urinary hemosiderin 0–4+	2+	3+	3+
Bone marrow			
Cellularity	Hyper	Hyper	Hypo
Myeloid/erythroid ratio	2/3	1/2	2.3/1
Ham test	+	+	+
Crosby test	+	+	+
Serologic abnormalities	Direct pos. Coombs (anti-globulin)	Serum acid hemolysin	0

*Indirect method (normal: 500,000–600,000).

CASE 2.—*PNH with concomitant transient acid hemolysin*

A 63-year-old business executive had suffered periodic respiratory infections for some years. Pallor and increasing fatigability were noted in March, 1954, and examination by his local physician disclosed mild icterus and considerable anemia (RBC 3.0 million). The diagnosis of acquired hemolytic anemia was made. Trials with corticotropin (ACTH), hydrocortisone, and cortisone failed to prevent a gradual decrease in hemoglobin level, and numerous transfusions were given. It was noted that apparently compatible blood caused severe hemolytic transfusions reactions with hemoglobinuria. No reactions occurred when washed red cell transfusions were given. Despite marked

TABLE 2.—*Special Serologic Investigations in Case 2*

A. Cold and Warm Isoagglutinin and Autoagglutinin Titers

	Patient's Serum					
	37 C.		22 C.		4 C.	
	Normal Cells	Own Cells	Normal Cells	Own Cells	Normal Cells	Own Cells
Saline	0	0	0	0	2,056	2,056
Albumin	0	0	16	32	256	512
Trypsin	0	0	0	0	----	512
Coombs	0	0	0	0	0	0

B. Cold and Warm Hemolysins

	Untreated Serum	Acidified Serum
1. Cold hemolysin (vs. trypsinized cells)	Neg.	+
2. Warm hemolysin (vs. trypsinized cells)	Neg.	+
3. Donath-Landsteiner	Neg.	

C. Ham Test

Untreated Serum		Acidified Serum		Heat Inactivated Serum		Heat Inactivated Serum Plus G.P.C.*	
Pt.	Control	Pt.	Control	Pt.	Control	Pt.	Control
0	0	3	1	0	0	0	0
0	0	3	0	0	0	0	0

*G.P.C. indicates lyophilized guinea pig complement (Difco).

salt restriction, steroid administration was followed by the development of marked peripheral edema. Mercurial diuretics did not result in significant diuresis, and acetazoleamide (Diamox) was prescribed. Ingestion of acetazoleamide tablets on three separate occasions was immediately followed by marked diuresis, severe bilateral flank pain, headache, precordial discomfort, and dizziness. On each of these three occasions, a large volume of dark red urine was excreted 10-24 hours following the acetazoleamide ingestion.

Examination at the New England Center Hospital in October, 1954, revealed moderate pallor and icterus and marked pitting edema of the lower extremities. The liver and spleen were not palpable. Routine laboratory data (Table 1) and additional erythrocytic and serologic studies (Table 2) suggested PNH very strongly. However, one of the tests using the patient's serum against normal red cells showed the presence of a peculiar acid hemolysin. The hemolysin was demonstrated at both 4 and 37 C and was active against both normal red cells and the patient's red cells. A cold agglutinin of high titre (512) was also present. In addition, the patient's cells were lysed upon exposure to normal acidified serum, suggesting a PNH-like intracorpuscular defect.

The administration of warmed washed erythrocytes was followed by further episodes of hemoglobinuria and failed to raise the homoglobin level. The patient was placed on cortisone therapy (200 mg. daily) and followed elsewhere. In the course of the next six months the concentration of the serum hemolysin gradually diminished, and eventually it could no longer be detected. The susceptibility of the patient's erythrocytes to acid hemolysis persisted, however, and thus all the laboratory data satisfied the strict criteria laid down by Ham for a positive test for PNH.[9] The patient continued to require numerous transfusions. He died in December, 1955, of homologous serum hepatitis.

CASE 3.—*Myelosclerosis with myeloid metaplasia terminating in PNH*

A 62-year-old sculptor from Kentucky was admitted to the New England Center Hospital in April, 1953. In May, 1952, he had begun to notice a slight exacerbation of his chronic nonproductive cough followed by the appearance of generalized joint pains and progressively increasing fatigability. A history of malaria and jaundice at age 17 and of tuberculosis at age 21 was elicited. No history of drug or chemical exposure could be established. His physician found normocytic anemia and splenomegaly, and a bone marrow biopsy disclosed a hypoplastic marrow. Cobalt proved ineffective, and the patient was placed on cortisone therapy, 25 mg. daily. This was of no benefit, and several transfusions were given without incident.

Physical examination was unremarkable except for mild pallor and moderate splenomegaly, and the spleen was felt 4 cm. below the left costal margin. Routine hematologic studies are given in Table 1. The blood uric acid was 6.3 mg. per 100 cc.

Several marrow aspirations obtained but little marrow, and a trephine marrow biopsy was performed, disclosing myelofibrosis, with an increase in reticulum cells and megakaryocytes. Splenic aspiration revealed developing erythrocytic and granulocytic precursors. These findings, in association with immature red and white cells and oval and tear-drop red cell forms in the peripheral blood, led to a tentative diagnosis of myelofibrosis with myeloid metaplasia.

The patient was discharged without medication and received intermittent blood transfusions. His course for a while was fairly satisfactory, but beginning in the summer of 1953, while staying in California, the patient developed severe reactions following transfusions. Each transfusion was followed in 8-12 hours by fever, jaundice, hemoglobinemia, and hemoglobinuria. The use of washed erythrocytes, however, minimized the reactions. There was an exacerbation of joint symptoms, with swelling about the joint of the toes, knees, and elbows. The blood uric acid level in August, 1953, was 7 mg. per 100 cc., and the patient was treated for gouty arthritis.

The patient was readmitted to the New England Center Hospital in October, 1954, for further evaluation. A dark urine specimen, strongly positive for hemoglobin, was passed during the night of admission. Subsequent investigations revealed hemoglobinemia, methemalbuminemia, and persistent hemosiderinuria. The Ham and Crosby tests were positive, establishing the diagnosis of PNH. It was felt that the large spleen was in part responsible for the increased rate of blood destruction. In view of several reports indicating the beneficial effects of splenectomy in selected cases of myeloid metaplasia,[27,28] it was decided to perform a splenectomy in the hope of removing one of the factors responsible for the increased transfusion requirement.

A liver biopsy was done and a lymph node also obtained at operation, and microscopic examination of spleen, liver, and lymph node showed striking erythroblastosis, with a few developing leukocytes and only rare megakaryocytes. Moderate hemosiderosis was also present. Bone marrow biopsy (rib) again revealed fibrosis. The postoperative course was a very stormy one and was complicated by pyelonephritis. The patient died of uremia three months postoperatively.

Comment

Two of the patients described above displayed serologic findings suggesting an autoimmune process, i. e., a positive direct

Coombs (antiglobulin) test in Case 1, and a serum (acid) hemolysin in Case 2, active against normal erythrocytes as well as those of the patient. Such hemolysins, especially of the cold variety, have been found in the serum of many patients with acquired hemolytic anemia [22]; however, the concomitant presence of an "acid" hemolysin present in the patient's serum has been previously observed in only one case [19] of PNH.

The simultaneous presence of both cell and serum abnormalities in Case 2 rendered serologic interpretation difficult. The diagnosis of PNH seemed logical, but the presence of an "acid" hemolysin which was active against normal red cells seemed to invalidate that diagnosis. This hemolysin was detected in both our laboratory and in that of Dr. William Valentine, of the University of California at Los Angeles.* After some months, however, the serum hemolysin could no longer be detected, and now all the strict criteria laid down by Ham for the diagnosis of PNH were present. The patient's course from then on was characteristic of PNH, although his death following a severe attack of probable homologous serum hepatitis was unexpected.

Investigation of previously reported cases of PNH reveals a fairly high incidence of auto- and isohemolysins and agglutinins. Four previous cases with positive Coombs (antiglobulin) reactions have been noted.[8, 15,17,19] Autohemolysins were present in five other cases [13,19,31-33] and type-specific isohemolysins in two additional instances.[34,35] Crosby [8] has cited five additional cases in which saline autoagglutinins were present. Liu described two cases of probable PNH in which the erythrocytes were unusually susceptible to both cold and acid.[36] In two cases leukoagglutinins have also been demonstrated.[12,19] This high incidence of associated immunologic abnormalities, together with the unique susceptibility of PNH cells to hemolysis by antibodies which merely agglutinate other cells,[37,38] suggest that immunologic mechanisms may play an important role in the pathogenesis of this disease. The fact that the defect is a corpuscular one, that it is acquired rather than hereditary, and that it is self-perpetuating has been somewhat obscured by the emphasis of many investigators on the normal plasma factors which aid in causing hemolysis of the cell. It should be emphasized that these factors are present in every normal plasma and that the fundamental defect of the erythrocyte has not been discovered. This is apparently acquired, chiefly in the third and fourth decades, in some instances earlier. Once present, it hardly ever disappears. There is no evidence of a hereditary basis or familial abnormality. In fact, in one case previously reported by one of us,[43] the patient was one of identical twins; her sister has remained well.

The possibility that PNH is an immunohemolytic disorder has already been broached by one of us in a previous article.[43] Such a mechanism might explain the effectiveness of steroid therapy in some patients with this disease.[5,11,13,15,19] In a case reported by Martin, there was an 18-month remission on steroid therapy during which time no transfusions were required.[1] Follow-up studies on a patient previously reported by one of us [5] reveal a sustained remission of three years' duration on steroid therapy.

Case 2 was of additional interest in that it illustrated the unique susceptibility of the PNH erythrocyte to minor alterations in body acid-base equlibrium. In this case, the administration of the diuretic agent acetazoleamide [8] produced severe hemoglobinuric exacerbations on three separate occasions. Acetazoleamide inhibits carbonic anhydrase in the renal tubule, thus depressing carbonic acid formation and consequently the H^+-Na^+ exchange in the renal tubule. As a result, bicarbonate reabsorption is incomplete, and the kidney elaborates an increased volume of alkaline urine. A mild metabolic acidosis therefore results and persists for as long as the drug is given. The effects following a single dose persist for about

* Dr. Valentine cooperated with us in this case.

six hours. Exacerbations of hemolysis following ingestion of several grams of acetylsalicylic acid, presumably due to slight decrease in body pH, have been noted previously.[4,5]

Case 3 presented with splenomegaly, fibrotic marrow, pancytopenia, immature red and white cells in the peripheral blood, and many oval and tear-drop red cell forms, i. e., the typical features of myelofibrosis with myeloid metaplasia. Splenic aspiration and later liver biopsy confirmed this diagnosis, although there was a preponderance of red cell precursors and relatively few granulocytes. The later development of gross hemolysis and hemoglobinuria following compatible transfusions eventually led to studies which confirmed the presence of PNH. Several possibilities are present to explain the findings of both myelofibrosis and PNH in the same patient. Crosby,[8] who saw the patient, suggested that the PNH lesion, which affects not only red cells but leukocytes and platelets and even the entire bone marrow in some instances, was responsible for the myelofibrosis in this case. Although myeloid metaplasia has been described in association with PNH in only one previous instance, it should be noted that aplastic or hypoplastic marrows have been noted in several previous cases.[3,4,13,40-42] It is therefore advisable to investigate all cases of atypical aplastic anemia or of myeloid metaplasia for the presence of the laboratory indications of PNH. Another possibility is that the PNH developed in this case as an immunologic abnormality following the numerous transfusions given for the underlying disease. We have seen another (transient) example of this in a man receiving numerous transfusions for chronic lymphocytic leukemia. Hemoglobinuria developed, and the red cell abnormalities characteristic of PNH were present for about two months, following which they disappeared.

These three rather atypical cases of PNH are therefore reported because it is well to remember that the fundamental erythrocyte defect of the disease has not as yet been elucidated, and thus any straws pointing in the direction of some etiologic possibility should be thoroughly investigated. In this paper, emphasis is placed upon the "immunologic straw."

Summary

Three cases of PNH with unusual clinical and serologic features are presented, bringing the number of reported cases to 183.

The presence of a possible autoimmune mechanism in two of the cases and in several previous reports, suggests that the erythrocyte defect in PNH may be due to an as yet undiscovered immunologic mechanism.

Acetazoleamide, a diuretic agent producing a state of mild acidosis, resulted in severe hemoglobinuria crises in one of the cases. Myelofibrosis with myeloid metaplasia was present in one case and probably antedated the development of PNH. This was first brought to light with the appearance of what appeared to be severe hemolytic transfusion reactions. The possibility is present that the PNH developed in this case as the result of a sensitization mechanism to numerous transfusions.

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Fatal Systemic Moniliasis Following Pancreatitis

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Candida albicans and related organisms rarely produce septicemia and widespread lesions which can be considered the immediate cause of death. The patient reported here developed C. albicans septicemia while recovering from severe pancreatitis. Broad-spectrum antibiotics given during the acute episode of pancreatitis probably allowed this organism to establish itself in necrotic areas of the pancreas and peripancreatic tissues. Oral nystatin * therapy failed to influence the rapidly fatal septic course.

Report of a Case

A 68-year-old single, white, retired laborer was admitted to the King County Hospital on Sept. 18, 1955, complaining of severe pain throughout the abdomen of 14 hours' duration. He had also noted low back pain and had vomited several times. He recalled two similar episodes within the preceding two years, but otherwise had been in good health. No dietary or alcoholic excess preceded the onset of abdominal pain.

The patient was moderately obese and appeared acutely ill. He was hiccoughing and repeatedly produced small watery emeses which contained occult blood. The patient's temperature was 101 F, the pulse was 120 and regular, and the blood pressure was 160/76. The abdomen was very tender, but there was no involuntary guarding. Bowel tones were hypoactive. There were no enlarged organs, no masses, and no gross evidence of ascites.

A roentgenogram of the chest showed some elevation of the right hemidiaphragm, and a survey film of the abdomen revealed blurring of the right renal and psoas shadows. Laboratory data included the following: hematocrit, 52; white blood cell count, 14,500, with increase in stab forms; urine protein, 200 mg. per 100 ml. The serum amylase was over 600 units (method of Smith and Roe[1]), the blood sugar was 144 mg. per 100 ml. (Benedict's method), and the icterus index was 25.

For the first three weeks of his five-week course the patient was treated with continuous gastric suction and parenteral methscopolamine.† Fluid and electrolyte balance was carefully maintained. Supplementary intravenous calcium, potassium, vitamins, and protein hydolysate were provided. Insulin was given during the first week whenever glycosuria was noted. One unit of whole blood was given after the hematocrit had fallen gradually to 36.

Broad-spectrum antibiotics were started on the third hospital day because of continued fever, with temperatures ranging from 100 to 103 F. This therapy was given for 21 days and consisted successively of intramuscular chloramphenicol, 500 mg. every eight hours for 4 days; intravenous tetracycline, 100 mg. every six hours for 10 days; and intramuscular chloramphenicol, 500 mg. every eight hours, for 7 days.

During the first week in the hospital, the patient developed paralytic ileus, ascites, and fixation of the right hemidiaphragm. After two weeks of severe illness, his condition gradually improved, and by the end of the third week he was free of symptoms except for weakness and anorexia. He was then afebrile, and the white blood cell count and serum amylase had returned to normal. Nasogastric suction was discontinued, and hourly antacids and oral methscopolamine were begun. Antibiotics were discontinued.

There was a small amount of purulent drainage from around a polyethylene intravenous tube at this time. The tube had been placed in the inferior vena cava via a femoral vein soon after admission. It was removed, and, because of continuing poor oral intake, another was placed in the opposite femoral vein and was left there for the remaining two weeks.

At the beginning of the fifth week, the patient's temperature began to rise and soon reached 106 F. He became confused and appeared severely toxic.

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* Mycostatin (E. R. Squibb & Sons).

† Pamine (provided by Joseph P. Webb, M.D., Department of Clinical Investigation, The Upjohn Company).

Blood cultures were taken. Guarding was noted in the right mid abdomen, but needle aspiration of the right paravertebral gutter failed to yield pus. There was no rise in the serum amylase or white blood cell count. Combined intramuscular chloramphenicol (Chloromycetin) and intravenous erythromycin therapy was given for two days. Urine cultures showed an Achromobacter in large numbers. When a heavy growth of Candida (Monilia) was seen in three blood culture bottles and on the blood pour plates, antibiotic treatment was changed to oral nystatin, 1.5 million units every six hours. However, high temperature and general deterioration of the patient's condition continued, and he died three and one-half days later.

Postmortem Examination.—Significant findings were limited to the abdominal cavity, which contained 150 ml. of clear fluid. The midtransverse colon was adherent to the mesentery. Breaking of these adhesions revealed an abscess cavity adjacent to the pancreas which contained pink fluid and necrotic tissue. The cavity extended from the midpoint of the pancreas left to the hilum of the spleen and from the posterior surface of the stomach around the inferior aspect of the pancreas to the anterior surface of the left kidney and adrenal gland. Although the stomach and pancreas were in contact with the abscess cavity, they appeared normal to gross inspection.

The liver weighed 2200 gm. and was somewhat yellow, with blurring of gross architectural details. The gallbladder appeared normal, and the bile ducts were patent, as were the pancreatic ducts. The renal capsules could be stripped without resistance. The exterior and cut surfaces of both kidneys were studded profusely with 1 to 2 mm. hemmorhagic areas. The spleen was abnormally soft.

Microscopic examination of the pancreas showed diffuse chronic inflammation and edema. There were small focal areas of necrosis in which many Monilia could be seen (Fig. 1). The numerous small renal abscesses also contained Candida (Figs. 2 and 3). Scattered monilial abscesses were seen in the myocardium (Fig. 4). The liver showed edema and areas of leukocyte infiltration compatible with acute toxic damage, but the architecture and most of the hepatic cells were normal; no Candida were observed.

Postmortem culture of the peripancreatic abscess grew C. albicans and coliform bacteria. Culture of the renal abscesses grew C. albicans only.

The organism isolated by blood culture was studied by Dr. B. S. Henry, of the Department of Microbiology, University of Washington School of Medicine. When it was grown on corn meal agar it produced many chlamydospores within 24 hours. Fermentation tests done according to the method of Martin[2] showed that the organism produced acid and gas from glucose and maltose in 24 hours and acid from sucrose after four days, and failed to ferment lactose. The production of chlamydospores and the fermentation tests served to identify this organism as C. albicans.

Comment

The patient reported above developed a peripancreatic abscess during an episode of acute pancreatitis. A prolonged course of broad-spectrum antibiotics probably suppressed the normal bacterial flora of the large bowel, which allowed overgrowth of C. albicans to occur. This organism apparently spread to the necrotic tissue surround-

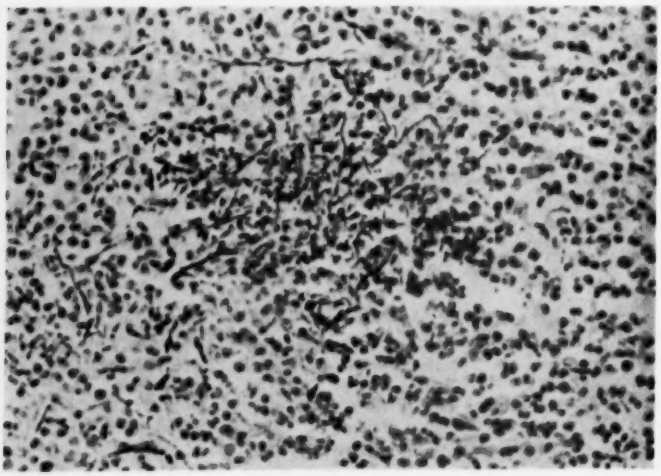

Fig. 1.—Pancreatic abscess showing Candida; Brown and Brenn stain; high magnification.

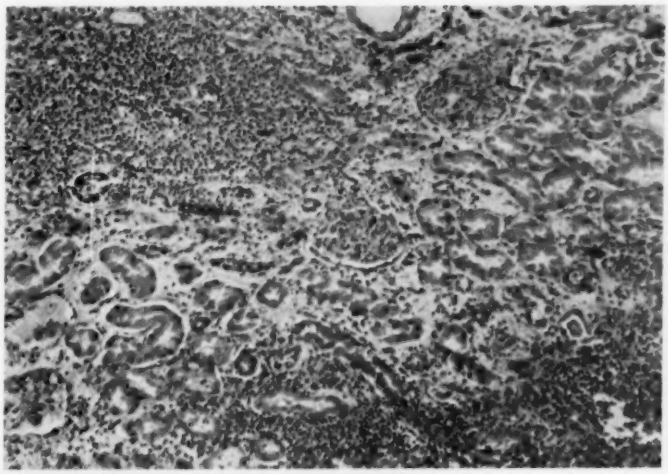

Fig. 2.—Renal tissue showing extensive abscess formation; hematoxylin and eosin stain; low magnification.

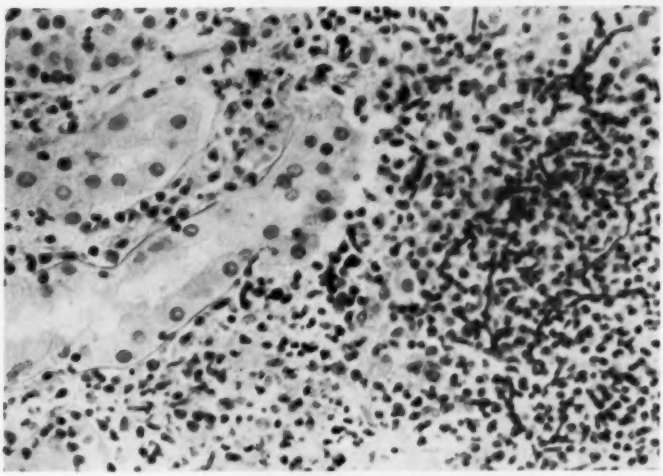

Fig. 3.—Abscess in renal tissue, showing Candida; Schiff stain; high magnification.

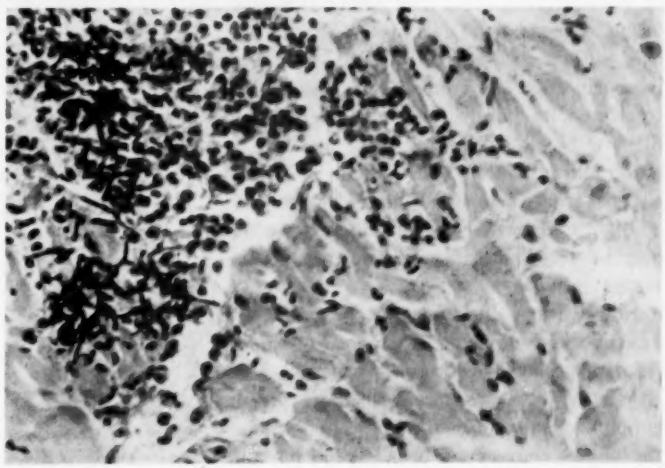

Fig. 4.—Monilial abscess of myocardium; Schiff stain; high magnification.

ing the pancreas and thence, via the blood stream, to the kidneys and myocardium.

Overgrowth of candida in the bowel and respiratory tract has been a major problem since the introduction of broad-spectrum antibiotics. Recent reports [3-5] suggest that when debilitated patients receive antibiotics for prolonged periods there is a risk that systemic moniliasis will develop. There has been a steady rise in number of cases of generalized moniliasis reported each year,[6] but it has not been conclusively demonstrated that this increase is causally related to the widespread use of broad-spectrum antibiotics.

Moniliasis of the deep tissues may present as a chronic bronchopulmonary lesion mimicking tuberculosis,[7] as a subacute mycotic endocarditis,[8] or as a central nervous system infection.[9] Infants of low vitality may develop massive spread of oropharyngeal moniliasis to the esophagus and lungs.[10] When monilial septicemia develops it is almost invariably fatal, and a common postmortem finding is innumerable mycotic abscesses of the kidneys and myocardium. However, there have been two reports [3,11] of patients who recovered from monilial septicemia. In neither case was recovery attributed to specific therapy, and both patients were left with monilial infections of the urinary tract.

Many therapeutic agents have been tried in systemic moniliasis, but none has proved to be consistently effective. Nystatin was used without effect in this patient. The drug is poorly absorbed from the gastrointestinal tract, and its failure may have been due to the low blood levels which are attained by oral administration. Preliminary reports suggest that Amphotericin,[12] or possibly brilliant green,[13] are fungicidal agents which may be useful in cases of deep tissue moniliasis.

Since drugs such as nystatin are quite effective in preventing or eradicating superficial monilial infections,[14] it would seem worth while to administer those agents prophylactically to debilitated persons when prolonged courses of broad-spectrum antibiotics must be given. Generalized moniliasis is such a rare entity that it would be very difficult to assess the effectiveness of such a program.

Summary

A case of fatal moniliasis, arising as a complication of pancreatitis with pancreatic abscess, is reported. Candida albicans was isolated from the blood during life and was demonstrated in the peripancreatic abscess, pancreas, kidneys, and myocardium at postmortem examination. The probable role of long-term, broad-spectrum antibiotic therapy in the development of this infection and the failure of oral mycostatin therapy to control it is discussed.

It is suggested that the concurrent use of a fungicidal agent be considered whenever broad-spectrum antibiotics are given in large doses for long periods of time.

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Clinical Diagnosis of Sickle-C Disease

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In 1949, Pauling reported that the hemoglobin molecule in sickle-cell anemia differed from normal adult hemoglobin.[1] Subsequently, a number of abnormal hemoglobins have been described. Numerically, the most important of these abnormal hemoglobins are S- and C-hemoglobin. When the two are present in the same person, a characteristic syndrome may occur, which is designated as sickle-C disease. The C-hemoglobin is said to occur in 2% of the American Negro population, either alone or in combination with other hemoglobin types.[2] Thus it is not rare, and an area which has a large Negro population may expect to see disorders arising therefrom. Until recently, the pathogenic significance of the heterozygous combination of S- and C-hemoglobins was not recognized, and the sickle trait was regarded as a completely benign, inherited abnormality of the erythrocyte. Through the work of Pauling[3] and others it became possible to identify other abnormal hemoglobins in patients who displayed the sickling phenomenon but whose illnesses did not follow the classical pattern of sickle-cell anemia. The most frequently seen pathogenic combination is sickle with C-hemoglobin. The present communication points up the clinical differences between sickle-cell anemia and sickle-C disease, which allow for a diagnosis prior to laboratory identification of the abnormal hemoglobin. In five cases of electrophoretically proven sickle-C disease a relatively uniform clinical picture was observed characterized by splenomegaly, the presence of numerous target cells, and complications typical of sickle-cell anemia, usually without significant anemia.

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Report of Cases

CASE 1.—The first patient, an 18-year-old Negro girl, had had recurrent episodes of muscular aches and cramps and occasional joint pains since the age of 6 (Table 1). At 14 she was seen at the University Hospitals with an ulcer of the skin of one of her fingers. Splenomegaly was noted and the patient showed a mild anemia. The patient was next seen on admission to the University Hospitals, in December, 1954, in labor with a normal-term pregnancy. The only noteworthy physical findings were a full-term pregnancy and an easily palpable spleen. Because of these findings, plus a positive sickle-cell preparation and numerous target cells in the peripheral blood, a diagnosis of sickle-C disease was made and later confirmed by electrophoretic study. Study of the parents of this patient revealed the father to have the C-trait and the mother, the sickle trait. The laboratory data of this as well as the subsequent cases are tabulated in Table 2.

TABLE 1.—*Clinical Features—Sickle-C Disease*

	Case				
	1	2	3	4	5
Athralgia	++	++	++		++
Abdominal cramps		+++	++		+
Splenomegaly	++		++	++	+
Complications					
Ulcerations	+				
Priapism		+			
Bone changes				+	
Optic atrophy			+		
Anemia	++	++			+

CASE 2.—A 12-year-old Negro boy had recurrent attacks of abdominal cramping pain since the age of 4. An appendectomy was performed a year later during one of these episodes. The pathological report is not available; however, similar abdominal pains have recurred frequently to the present. On one occasion of abdominal distress

TABLE 2.—*Laboratory Findings—Sickle-C Disease*

	Case				
	1	2	3	4	5
Hemoglobin	8.7	8.2	13.8	12.2	10.4
Hematocrit	30	31	36	40	
Red cell count	3.0	3.0	3.7	4.1	3.7
White cell count	6,600	14,000	10,000	16,100	18,300
Reticulocytes, per cent	2.3	4	3.4	3	2.4
Target cells, per cent	80	60	80	30	50
Sickling					
1. Direct smear	—	—	—	—	—
2. Metabisulfite	+	+	+	+	+
Fetal hemoglobin, per cent	2.1	10.8	4.7	10	4
Osmotic fragility		↓	↓	↓	
Bone marrow		Ery. Hyp.	Ery. Hyp.	Ery. Hyp.	Ery. Hyp.

the patient had a gross rectal hemorrhage. Since the onset he had recurrent cramping pains of the muscles of his legs and occasional joint pains. He was admitted to Crippled Children's Hospital in 1955 because of severe priapism which developed following a dermatitis of the legs and perineal region. Nothing unusual was found on physical examination except the priapism. Because of the history and the finding of many target cells in the peripheral blood, a clinical diagnosis of sickle-C disease was made and confirmed. Only one parent is known, and she has the C-trait.

CASE 3.—A 10-year-old Negro girl was found at the age of one to have unexplained optic atrophy. At 3 she began having intermittent attacks of cramping abdominal distress associated with muscular pains. She was seen in our emergency room in 1955 because of a severe episode of cramping periumbilical pain. Physical examination revealed an external strabismus, a Grade 2 systolic murmur at the apex, a palpable liver edge, and moderate splenomegaly. Inspection of a peripheral blood smear showed 80% target cells, and the patient was admitted to Crippled Children's Hospital with the diagnosis of sickle-C disease. Her father is dead, and her mother is heterozygous for S-hemoglobin.

CASE 4.—A 6-year-old Negro girl, a sibling of Case 3, has had no symptoms to date but was examined after the diagnosis was made in her sister. On examination she was found to have marked splenomegaly and numerous target cells in the peripheral blood. X-ray studies of the long bones and skull revealed granular osteoporosis and rarefaction typically found in long-standing erythroid hyperplasia. Subsequent laboratory examinations as noted in Table 2 revealed the characteristic finding of sickle-C disease.

CASE 5.—A Negro boy was first admitted to Crippled Children's Hospital at 18 months of age because of abdominal pain and distention. At the age of 2 years, the patient began having muscular aches and joint pains involving primarily the elbows and shoulder girdle. The only pertinent physical finding was a palpable spleen tip.

Thus it can be seen in Table 2 that three patients had a moderate anemia which was normochromic and normocytic. By our laboratory standards all of the patients showed a modest reticulocytosis. Leukocytosis was variable in degree, but in general there was a strong tendency to a myeloid shift. On a stained smear the erythrocytes had a uniform appearance which was impressive, showing from 30% to 80% target cells in every case.* This we feel is a very important and useful finding in the differential diagnosis. Each patient showed sickling in a metabisulfite preparation. A typical electrophoretic pattern showing both S- and C-hemoglobins was demonstrated in each. The amount of fetal hemoglobin varied from 2% to 10%. All marrows examined showed erythroid hyperplasia, and three of the bloods examined showed decreased osmotic fragility to hypotonic saline.

During the period of this study we have had the opportunity to see 16 cases of electrophoretically proved sickle-cell anemia (SS). These afford an excellent point of contrast with patients having sickle-C disease. Certain representative data from the patients with sickle cell anemia are tabulated in Table 3. In addition to the items tabulated in this Table, all cases presented intermittently arthralgia, abdominal cramps, icterus, frequent clinical crises, and such complications as noted. Splenomegaly was not observed in any of these cases. In 15 of the cases, spontaneous sickling plus marked anisocytosis and poikilocytosis was

* Large numbers of target cells are also seen with hemoglobin D.*

TABLE 3.—*Sickle-Cell Anemia—Representative Observations**

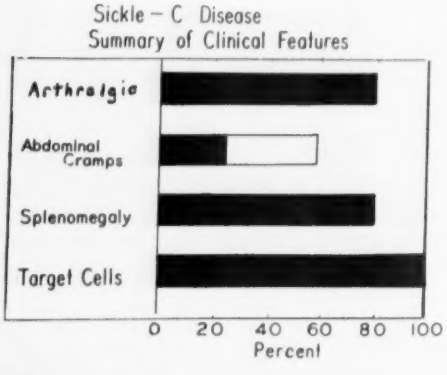
Case No.	Age, Yr.	Hgb., Gm.	WBC, 10^3	Retic, Per Cent	Sickle†	Target‡	Spleen	Comment
1	10	5	16	8	+	0	0	Salmonella osteomyelitis
2	17	10	11	?	+	+	0	No history of crises
3	30	5	17	?	+	0	0	Three living children
4	14	9	11	1	+	0	0	Identical twin of Case 5
5	14	7	13	?	+	+	0	
6	24	6	14	5	+	5%	0	Leg ulcers
7	4	8	19	18	?	?	0	
8	4	6	31	16	+	0	0	
9	24	7	15	8	+	+	0	Leg ulcers
10	16	8	18	?	+	+	0	"Legg-Perthes"
11	18	6	15	4	+	0	0	Leg ulcers
12	1	9	25	?	+	0	0	Osteomyelitis
13	4	8	23	?	+	0	0	Rectal bleeding
14	26	5	12	20	+	+	0	One living child
15	41	4	20	4	+	0	0	Died in congestive failure
16	21	7	21	5	+	+	0	Pregnant, 8th month

*All cases electrophoretically proved to be homozygous S-S.
†Cases marked positive showed sickling on dry smear. All cases showed sickling with metabisulfite preparations.
‡Cases only noted as positive had too few target cells to prompt a percentage estimate.

noted on the dry blood film. Although target cells were noted in seven instances, their relative number was consistently few. In addition, one case of thalassemia-sickle-cell disease was seen in a 60-year-old Negro woman. This patient showed a moderate anemia and diffuse bony changes of chronic erythroid hyperplasia. Her spleen was not palpable. The peripheral blood smear was remarkable for hypochromia and aniso- and poikilocytosis, but only 10% of the erythrocytes were of the target form.

Comment

Although there appears to be rather wide variation in the severity of sickle-C disease, the principle clinical features seem to be quite constant. The comparison which follows is based on the five cases reported above as well as on 41 cases of sickle-C disease previously reported in the literature.[2,4-8] As indicated in the Figure, arthralgia is the most consistent symptom and may vary from severe monarticular arthritis with a hot swollen joint to vague knee and elbow pains. Associated with joint pains diffuse muscular aching occurs frequently, especially in the lower legs and back. These complaints have been a major symptom in 80% of both our cases and those reported in the literature. Ulceration has been seen infrequently. It has been reported previously in one case, and we have seen it in but one of our cases.



Intermittent abdominal cramps, with or without hemolytic crises, have been frequent, and this symptom may, at times, be severe enough to stimulate an acute surgical condition. Several instances are reported of laparotomy for appendicitis with no demonstrable disease being found. Characteristically the patients have complained of diffuse epigastric and periumbilical cramping lasting for several days, which subsides gradually. There are no associated gastrointestinal disturbances. These symptoms occurred in three of our five patients. As represented by the solid bar in the Figure, this symptom has been encountered less frequently in previously reported cases of sickle-C disease.

Splenomegaly has been reported in 80% of the reported cases, including ours. In the majority of these the spleen was palpable more than 4 cm. below the left costal margin. In general the older the patient the

more consistent the finding of splenomegaly and the greater the enlargement. Crises apparently are associated with a transient increase in the size of an already enlarged spleen. This frequency of splenomegaly is in direct contrast to the small and often atrophic spleen of sickle-cell anemia. It is known that many of the previously reported cases of "sickle-cell anemia" with splenomegaly have been found to be sickle-C disease. It seems probable that the diagnosis of sickle-cell anemia in a patient with splenomegaly should be made with a great deal of caution.

The presence of target cells in the peripheral blood has been associated with hemoglobinopathies connected with C-hemoglobin since its discovery. In all cases of sickle-C disease adequately described, target cells have been noted, and almost invariably more than 30% of the erythrocytes are of the target form. Anemia has been a more variable finding. When present it is usually microcytic, normochromic in type, and of moderate severity. Hemolytic crises, although not as common as in sicklemia, do occur and at times are of major importance. Slight but definite reticulocytosis is usual, and increased demand on the bone marrow, as evidenced by erythroid hyperplasia, is evident. Fetal hemoglobin occurs in excess of 2%, as measured by determining the amount of alkaline-resistent hemoglobin present.

Although radiologic studies were of little value in the five cases presented here, it is interesting that 7 of the 41 cases reviewed had aseptic necrosis of the femoral heads. One of our patients showed diffuse demineralization characteristic of chronic erythroid hyperactivity.

Summary

The clinical features of five cases of sickle-C disease are described, and 41 previously reported cases are reviewed. These data are contrasted with 16 cases of electrophoretically proved sickle-cell anemia. It is felt that when a Negro patient with a positive sickle-cell preparation has the findings of (1) arthralgias, (2) abdominal cramps, (3) splenomegaly, and (4) more than 30% target cells in the peripheral blood that an accurate clinical diagnosis of sickle-C disease is possible.

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Hematemesis and Melena Complicating Treatment with Rauwolfia Alkaloids

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Alkaloids of Rauwolfia serpentina, especially reserpine, are being used widely in the treatment of hypertension and mental illness. In addition to their pharmacologic actions on the cardiovascular and central nervous systems, a variety of effects have been reported on the gastrointestinal system. Both gastric secretory and motor activity in dogs are augmented by reserpine.[1] Increased volume and acidity of gastric secretions has also been found in man under the influence of reserpine.[2,3] Hypermotility of the lower gastrointestinal tract is clinically evident in the occasional complaint of diarrhea in patients taking the drug. Emetic effects, suggesting hypermotility of the upper gastrointestinal tract, have been reported in animals and man.[4] These actions on the gastrointestinal tract, produced in the main by the cholinergic-like action of the drug, suggest that duodenal ulcer might be activated. Such activation of ulcer in patients receiving reserpine has been reported.[4]

Hematemesis and melena associated with the use of reserpine have been previously mentioned, but the circumstances were such that a direct causal relationship could not be established.[2] Three of the cases to be presented occurred among over 600 patients treated for mental illness with large doses of various Rauwolfia preparations. The fourth case had been treated for hypertension with the drug. Although this complication must be rather rare, its potential seriousness merits consideration whenever these drugs are to be used in large doses or for prolonged periods of time.

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From the Medical Service, Veterans Administration Hospital.

Technical assistance for the studies on blood clotting was given by Vernon L. Henrich, B.S., and Saul L. Kanter, B.S.

Report of Cases

CASE 1.—This 25-year-old man with a schizophrenic reaction was started on reserpine on April 24, 1955. In 1953, he had complained briefly about abdominal pain. A gastrointestinal series on Oct. 20, 1953, had been reported as negative. His general health was excellent.

A single oral dose of 12 mg. of reserpine was given by error on the first day of treatment. The patient soon developed severe vomiting and retching in addition to a marked cutaneous flush. These symptoms subsided in about 36 hours. A gastrointestinal series on April 27, 1955, indicated probable reflux esophagitis. On April 29, treatment was resumed with a daily parenteral dose of 5 mg. of reserpine followed soon by an oral dose of 3 mg. daily. He seemed to tolerate this program of treatment well. The daily oral dose of drug was increased to 6 mg. on June 11. On July 4, he returned to the hospital from a leave of absence complaining of abdominal distress. Soon after, he vomited a large amount of blood and passed a large bloody stool. His blood pressure quickly fell to 80/45, but his pulse rate did not exceed 100 despite the manifest clinical signs of shock. The erythrocyte count declined to 2.65 million, the hemoglobin to 8.5 gm. per 100 ml., and the packed cell volume to 26%. He received morphine, intravenous dextran solution, whole blood transfusions, and parenteral diphemanil methylsulfate (Prantal). Shock responded readily to treatment after 2000 ml. of whole blood and 2000 ml. of 6% dextran solution had been given. He was started soon on a Sippy regimen with methscopolamine (Pamine) bromide and phenobarbital given orally. A gastrointestinal series on July 11 again showed probable reflux esophagitis, with no evidence of ulceration.

Treatment with a daily dose of 400 mg. of chlorpromazine orally was started on July 29. On Sept. 22, while on both chlorpromazine and methscopolamine bromide, he developed a large fecal impaction. With some reduction in dosage of each drug, he has continued without further symptoms.

CASE 2.—This 64-year-old man with a chronic schizophrenic reaction was started on reserpine on Aug. 15, 1955. His previous health had been excellent. He received 5 mg. intramuscularly for seven days, with an oral dose of 3 mg. daily being started on Aug. 17.

On Aug. 20 he had several episodes of hematemesis, vomiting 200-300 ml. of blood each time. His blood pressure declined to 100/60, pulse rate was 80, and only mild clinical signs of shock were observed. The packed cell volume remained at 47%. He was treated with intravenous saline solution, parenteral diphemanil methylsulfate, and phenobarbital sodium. The following day he was started on a bland diet and methscopolamine bromide and phenobarbital were continued orally. No further bleeding occurred.

A gastrointestinal series on Aug. 24 showed evidence of a hiatus hernia without any ulceration, but with enlarged rugae. Reserpine was resumed on Aug. 30, at a daily dose of 1 mg., and has been continued without further adverse effects. An anticholinergic drug was continued along with the reserpine.

CASE 3.—This 62-year-old man with a chronic schizophrenic reaction was started on tranquilizing medication on Feb. 10, 1956. Except for his chronic psychosis, his general health was good. He had an episode of vomiting associated with a fecal impaction a few weeks before treatment was begun.

He was started on a preparation containing all the alkaloids of Rauwolfia serpentina with most of the reserpine removed, receiving 20 mg. three times daily by mouth. This preparation, similar to large doses of reserpine, produced a marked cutaneous flush and mucous membrane injection. He seemed to be doing well until Feb. 17, 1956, when he suddenly collapsed after having a massive hematemesis. Within a short time he passed a large amount of tarry stool and had several more hematemeses. His blood pressure became unobtainable, but the pulse rate never exceeded 100. Shock was treated with infusions of 6% dextran solution followed quickly by transfusions of whole blood. Mephentermine (Wyamine) sulfate, oxygen, phenobarbital (Luminal) soduim, and digoxin were also used. Despite the transfusion of blood under pressure through both femoral arteries, he remained in shock for 24 hours. Repeated hematemeses and massive melena occurred during this period. His blood pressure reached a borderline level on the second day, but promptly fell to shock levels with each new hematemesis or bloody stool during the next three days. Black liquid stools persisted for another five days, but no new hematemesis occurred. The erythrocyte count declined to 2.26 million, with a hemoglobin of 6 gm. per 100 ml. Blood urea nitrogen rose to 102 mg. per 100 ml. but quickly fell to normal when the bleeding ceased. Altogether, he received 10,000 ml. of whole blood before signs of hemorrhage stopped and his erythrocyte count was restored to normal.

As soon as feasible, he was started on a Sippy regimen with parenteral doses of an anticholinergic drug. A gastrointestinal series on March 1 was not satisfactory because of the presence of residual clots in the stomach. This examination was repeated on March 6, no abnormalities being found. His subsequent course has been satisfactory, without evidence of further bleeding.

CASE 4.—This 64-year-old man was admitted to the hospital on Feb. 18, 1956, because of hematemesis and melena. He had never had these symptoms before, though 25 years previously he had bled from hemorrhoids. For the past 11 months he had complained of intermittent epigastric pain, sometimes associated with vomiting. The day of admission he vomited dark liquid material, and soon after he passed a soft black stool.

He had been started on treatment for hypertension on April 4, 1955. Alseroxylon fraction of Rauwolfia serpentina was administered in daily doses of 8 mg. until July 8, 1955. At this time he was placed on a daily dose of reserpine, 0.6 mg., and hydralazine, 150 mg., which was continued until Jan. 19, 1956. On this date his medication was changed to a daily dose of reserpine, 0.5 mg., and protoveratrines A and B, 2.0 mg. He was taking this medication when he entered the hospital.

After admission (Feb. 18, 1956), he had one small hematemesis and a large soft black stool. Both specimens were strongly positive for blood. He complained of epigastric pain and tenderness, but no further evidence of bleeding was observed. His blood pressure was slightly elevated, his pulse within normal limits. Determination of the erythrocyte count was 4.72 million, the packed cell volume was 39%, and the hemoglobin, 11.5 gm. per 100 ml.

He was started on a progressive Sippy regimen, supplemented by methscopolamine bromide and phenobarbital. A gastrointestinal series on Feb. 24 showed an active duodenal ulcer. With continued treatment and discontinuation of the Rauwolfia medications, he showed symptomatic improvement. A gastrointestinal series on March 28 revealed a healed duodenal ulcer.

Additional Studies on Reserpine and Blood Clotting

The possibility that reserpine has some direct effect on blood clotting was raised

by a report of failure of blood to clot and lengthening of the prothrombin time in patients on the drug, as well as inhibition of in vitro clotting by the addition of reserpine.[5] To study such effects, we selected patients who had been on reserpine for two months or more and whose daily dose of the drug was 2 mg. or more.

Blood clotting and clot retraction were observed to be normal in 148 such patients. Determinations of prothrombin time were performed in 105 reserpine-treated patients and 32 control patients. The distribution of results was similar between the two groups, the lowest value for prothrombin activity in either group being 60%. The fall in prothrombin activity 48 hours after a single dose of 200 mg. of bishydroxycoumarin was compared in 21 reserpine-treated patients and 18 controls. The degrees of change were comparable between the groups and were not excessive. Capillary fragility tests were performed on 68 reserpine-treated patients. The test was negative in 56, equivocal in 10, and positive in two patients. Platelet counts in the 2 patients with positive tests and in 5 of the 10 patients with equivocal tests were normal. Bleeding and clotting times were normal in all 12 patients with equivocal or positive capillary fragility tests.

Comment

Each of the four patients experienced hematemesis and melena for the first time during treatment with reserpine or other alkaloids of Rauwolfia. The close time relationship between the onset of treatment and these symptoms in Cases 2 and 3 makes chance coincidence an unlikely explanation. The rather high doses of drugs used in the first three cases produced this complication early in the course of treatment, while the smaller doses of reserpine used in Case 4 did not evoke symptoms until later. The possibility of a preexisting duodenal ulcer in the latter case can not be excluded. Although reserpine was the alkaloid responsible for hematemesis and melena in three of these cases, the preparation containing all the alkaloids of Rauwolfia used in Case 3 produced a similar complication. Thus, other alkaloids of Rauwolfia besides reserpine may also produce this effect.

The most tempting explanation of these effects is to postulate the development of peptic ulceration aggravated by the drugs. However, clear-cut evidence of such ulceration occurred only in Case 4, and the possibility that such ulceration existed before treatment could not be excluded. Even without postulating the development of the usual type of peptic ulcer, the possibility remains that the combination of hypersecretion and hypermotility induced by these compounds could cause acute gastric erosions. If such erosions occurred in a mucosa which was the site of marked vasodilation, such as these drugs produce in the skin and visible mucous membranes, then massive hemorrhage might occur. Gastroscopic studies of the appearance of the stomach mucosa after use of these drugs would be most helpful in explaining such a possible mechanism.

A remote possibility exists that hematemesis and melena could be the result of some systemic disorder of blood clotting induced by these drugs. The absence of any other clinical evidence of bleeding in these patients makes such an explanation unlikely. Our own studies and others of which we are aware have failed to show any evident or consistent change in blood clotting of patients treated with large doses of reserpine for prolonged periods. The discovery that reserpine increases the excretion of a serotonin metabolite raises the possibility that some qualitative change in blood platelets might occur due to serotonin depletion.[6] Here, too, one would expect that widespread systemic hemorrhage would be present. So far, the available evidence suggests that hematemesis and melena are due to local changes in the gastrointestinal mucosa rather than a disorder of blood coagulation.

The complication of hematemesis and melena during treatment with alkaloids of Rauwolfia serpentina is unusual enough to make this risk worth taking if the clinical

indications for these drugs are strong enough. In patients with known ulcerative disease of the gastrointestinal tract or hemorrhagic diatheses, it would appear that these compounds are contraindicated unless closely covered by other treatment or laboratory control. Patients under treatment with large doses of these drugs for prolonged periods of time should be observed closely for any symptoms suggesting the development or activation of peptic ulcer.

Summary

Four cases of hematemesis and melena are reported which occurred during treatment with alkaloids of Rauwolfia serpentina. The lack of antecedent gastrointestinal hemorrhages and the close time relationship of these symptoms to the use of these drugs makes a causal relationship likely. Although reserpine may cause exacerbation of duodenal ulcer, frank ulceration was found by roentgenologic examination in only one of these patients. The hypermotility, hypersecretion, and vascular dilatation of the gastric mucosa produced by these drugs are thought to cause small gastric erosions which may bleed profusely. No evidence was found that these drugs cause a disorder of blood clotting. Gastrointestinal ulceration or hemorrhagic diathesis are contraindications to the use of these preparations unless the clinical indication is sufficiently great and close observation is possible.

Since submission of this paper for publication, the following report of a similar complication has also appeared: Dillon, D., and Swain, J. M.: Gastro-Intestinal Hemorrhage as a Complication of Reserpine Administration: Report of 2 Cases, *Am. J. Psychiat.* 113:462 (Nov.) 1956.

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Treatment of Mumps Orchitis with Adrenal Hormones

Report of Twenty-Three Cases with a Note on Hepatic Involvement in Mumps

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Epididymo-orchitis occurs as a complication in the course of mumps in 18% to 43% of postpubertal males.[1-4] Not only is gonadal involvement accompanied by severe local pain and systemic discomfort, but testicular atrophy is a sequel in about one-half of the cases, and sterility can result, although this is probably unusual.[5,6] Of the various prophylactic measures that have been tried in males with epidemic parotitis, the administration of diethylstilbestrol has given encouraging results,[7,8] and early injection of γ-globulin prepared from mumps convalescent serum has resulted in definite reduction in the incidence of orchitis.[9] The treatment of established orchitis, however, has remained unsatisfactory. Antibiotics,[10-14] pooled plasma,[15-17] convalescent serum,[18] estrogens,[7] and surgical decompression[19-21] have been irregularly effective. At present, the usual regimen consists of analgesic and antipyretic drugs with local application of cold and the use of various suspensory devices.

The few available descriptions of the histologic characteristics of mumps orchitis[20] indicate that distention of seminiferous tubules by inflammatory exudate, edema of intertubular connective tissue, swelling of the tunica albuginea, and acute hydrocele[22] combine to produce pressure necrosis of the gonad. This supports the clinical impression that swelling of the testicle within its unyielding tunics is the major factor responsible for acute pain and subsequent atrophic changes. This concept, of course, is the rationale for surgical decompression.

The remarkable anti-inflammatory properties of the adrenal steroids as well as their efficacy in alleviating a variety of "febrile toxemic" states suggested that these hormones might be useful in the management of mumps orchitis. The present report summarizes our experience with the use of cortisone and related compounds in the treatment of 23 cases of mumps orchitis during the past four years.

Clinical Material

The 23 patients with mumps orchitis that form the basis of this report were observed during a period of four years on the Emory University Medical Service at Grady Memorial Hospital, Atlanta; the Yale University Medical Service, Grace-New Haven Hospital, New Haven, Conn., and the Osler Medical Service, The Johns Hopkins Hospital, Baltimore. They ranged in age from 13 to 44 years. All cases were sporadic; no true epidemic occurred during the period of study. In none of the hospitals where the study was carried out is it customary to admit patients with uncomplicated epidemic parotitis.

Examinations of cerebrospinal fluid, liver function tests, serum amylase determinations, and mumps complement-fixation tests were carried out in several, but not all, patients.

The results of adrenal steroid therapy were noted and recorded carefully during the acute disease. Later follow-up examinations were possible in only 14 cases. There was considerable variation in dosage of hormones in individual cases during the period of the study, depending upon several factors, including availability of drugs, expense, and response to treatment.

The pertinent data for the 23 cases are summarized in Table 1.

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TABLE 1.—*Clinical Course of Mumps Epididymo-Orchitis Treated with Corticosteroids*

Case	Age	No. Days After Onset of Parotitis	Gonad Involved	Rigor at Onset	Max. Temp., F	Adm. WBC, 10^3/ Mm.	Abd. Pain	Serum Amylase, Units†	CSF Cells, Mononuc. /Mm.†	CSF Protein Mg./100Cc†	Mumps C.F. Test, Reciprocal†	Duration of Orchitis Before Treatment, Days	Total Dose of Hormone†	Duration of Therapy, Days	Time for Deferves-cence, Hr.	Testicular Improvement‡	Symptomatic Improvement‡	Remarks
1	38	Simult.	B	0	104.6	10.3	+	Normal§	ND	ND	32	5	950C	6	36	4+	4+	No follow-up
2	28	7	B	0	106.0	22.0	+	Normal§	ND	ND	16	3	1100C	9	12	4+	4+	Azoospermia at discharge; no atrophy at 6 mo.
3	23	7	B	0	104.8	18.7	+	ND	45	22	64	1	700C	7	24	4+	4+	No atrophy at 12 mo.
4	18	1	B	+	104.0	23.0	+	Normal	ND	ND	ND	4	875C	7	72	3+	3+	Azoospermia at 12 mo.
5	14	6	B	0	105.1	17.8	0	500§	ND	ND	ND	1	400A	4	12	3+	3+	No follow-up
6	22	3	B	0	104.6	4.7	+	Normal§	ND	ND	0	2	1075C	7	36	3+	3+	No atrophy at 2 mo.
7	29	5	R	0	105.0	10.2	0	ND	ND	ND	ND	2	1275C	7	60	3+	3+	No follow-up
8	30	10	L	0	104.0	15.9	+	ND	ND	ND	ND	4	1450C	10	72	4+	4+	No follow-up
9	22	6	R	0	104.0	3.4	+	260§	ND	ND	64	2	750C	5	30	4+	4+	Slight atrophy at 1 mo.
10	25	7	R	0	103.6	11.0	0	416§	ND	ND	ND	0	4100C	18	48	2+	2+	Atrophy at 2 mo.; orchitis while on cortisone
11	44	6	R	0	106.6	9.4	0	ND	ND	ND	40	2	1350C	9	36	3+	3+	No atrophy at 1 mo.
12	20	4	R	0	104.2	10.9	+	282§	ND	ND	±	4	1750C	15	24	4+	4+	No follow-up
13	17	5	L	0	104.2	12.5	0	420§	Normal		ND	2	1100C	7	24	4+	4+	No follow-up
14	17	1	B	+	107.0	5.2	+	730 (P)	38	12	40	6	1550C	10	104	4+	2+	No follow-up
15	42	1	B	0	104.4	6.2	+	285 (P)	ND	ND	160	5	1375C	8	60	4+	2+	No follow-up
16	32	6	R	0	104.2	9.2	0	ND	ND	ND	20	1	185M	6	12	4+	4+	No atrophy at time of discharge
17	27	No parotitis	R	0	105.2	8.8	+	Normal	98	Pandy 0	64	2	500C	3	24	4+	4+	No atrophy at 3 mo.
18	25	6	R	0	102.0	9.9	0	333§	40	Pandy 0	32	0.5	550C	3	24	4+	4+	No atrophy at 1 mo.
19	26	5	R	0	100.0	17.1	0	Normal	Normal		ND	3	800C	4	12	4+	4+	Atrophy at 2 mo.
20	18	7	L	+	104.0	18.8	+	566 (P)	62	Pandy 1+	ND	3	700C	5	54	4+	2+	Atrophy at 6 mo.
21	29	Simult.	B	0	104.8	14.8	0	ND	21	Pandy 0	ND	3.5	650C	4	8	4+	4+	Father ×2
22	13	3	L	+	104.8	14.0	0	ND	13	ND	ND	4	525C	5	20	4+	4+	No follow-up
23	13	6	R	0	104.2	10.1	0	ND	27	Pandy 1+	ND	1	600C	4	12	4+	4+	No atrophy at 6 mo.

*B indicates bilateral orchitis; L, left testicle inflamed; R, right testicle inflamed.
†ND indicates not done; C, Cortisone; A, ACTH (units); M, prednisone (mg.); P, pancreatitis; Normal, serum amylase <150 units.
‡4+ indicates dramatic relief; 3+, good relief; 2+, fair relief.
§Parotitis still present.

Clinical Aspects of Orchitis

Relationship to Parotitis.—Orchitis was preceded by parotitis in 20 of the 23 cases, the interval between onset of parotid swelling and testicular involvement ranging from 1 to 10 days. In two of the other three patients, parotitis and orchitis were simultaneous in onset. In the remaining patient (Case 17) there was no evidence of salivary adenitis at any time, although the diagnosis of mumps was suspected from history of definite exposure and the presence of cerebrospinal fluid pleocytosis. This clinical impression was confirmed by a rise in complement fixation titer for mumps to 1:64.

Fever.—Fever was a prominent manifestation in all 23 patients. Chilly sensations were the rule at onset, and in four cases, at least one true rigor occurred. The maximum temperature averaged 104.4 F for all cases, and in only three patients did the temperature fail to reach 104 F during hospitalization; in six cases, the maximum recorded ranged from 105 to 107 F.

Local Signs.—Testicular involvement was unilateral in 14 cases (61%) and bilateral in nine (39%). This is a somewhat higher incidence of bilateral disease than is generally reported, but these were selected cases in that the presenting complaint in all but one instance was orchitis. Involved gonads were swollen, tense, and exquisitely tender. In most cases, the epididymis was easily palpable as a swollen, tender cord, bearing out the findings of Candel [23] regarding the frequency of involvement of this structure in mumps orchitis.

Pancreatitis and Meningitis.—Although abdominal pain was a prominent symptom in 12 patients, the combination of upper abdominal pain, nausea, vomiting, and elevation of serum amylase in the absence of parotitis made the diagnosis of pancreatitis likely in only three patients.

While no patient in this series had signs of meningeal irritation or focal neurologic signs, headache was common and spinal fluids of several patients showed pleocytosis.

Laboratory Findings.—Peripheral leukocyte counts ranged from 3400 to 23,000 per cubic millimeter, with a mean of 12,400. Leukocytosis was due to increase in polymorphonuclear cells. In 15 patients the initial counts were higher than 10,000, and in 7, exceeded 15,000. Of 15 serum amylase determinations, nine were elevated (Table 2). Spinal fluid was examined in 10 cases. Pleocytosis ranging from 13 to 98 mononuclear cells per cubic millimeter was found in eight; the protein content of the spinal fluid was generally within normal limits.

TABLE 2.—*Summary of Relationship Between Abdominal Pain, Parotitis, and Serum Amylase in Fifteen Cases of Mumps*

Manifestations		Serum Amylase	
Parotitis	Abdominal Pain	Normal	Elevated
+	+	3	2
+	−	1	4
−	+	1	3
−	−	1	0

Mumps complement-fixation tests were performed on one or more occasions in 12 cases and a positive titer obtained in 11. Laboratory data are detailed in Table 1.

Liver Function in Mumps Orchitis.—The finding of hepatosplenomegaly in one patient (Case 2) and splenomegaly in another (Case 3) with associated abnormalities in liver function tests in both patients focussed attention upon the possibility of hepatic involvement in mumps. Tests of liver function were carried out in 11 of the 23 cases in the study. The results of these are presented in detail in Table 3 and summarized in Table 4. In two patients, (Cases 10 and 15), all tests were normal. In four (Cases 7, 12, 14, and 16) a mild, or "borderline," abnormality in the form of impairment of sulfobromophthalein (Bromsulphalein) clearance, elevation of serum bilirubin, or increase in serum alkaline phosphatase was found. In the remaining five patients (Cases 1, 2, 3, 4, and 6), derangement of function was indicated by two or more of the tests employed. Cases 2 and 3 were brothers; in both there was splenomegaly, elevation of indirect serum bilirubin,

TABLE 3.—*Details of Liver Function Tests in Eleven Cases of Mumps Orchitis**

Case	Days After Onset of Orchitis	Bilirubin, Mg./100Cc. Dir.	Bilirubin, Mg./100Cc. Total	BSP, % 45 Min.	Ceph. Floce. 24 Hr.	Ceph. Floce. 48 Hr.	Thymol Turb.	Thymol Floce.	Alk. Phos., Units	Urine Urobil.	Urine Bile
1	3	0.22	1.08	22	3+	3+	3.7	1+	2.8	0.70	0
2	1	0.37	2.28	9.8	3+	3+	2.6	0	3.8	8.55	0
	5	0.11	1.08	ND	3+	3+	1.9	0	4.7	0.17	0
	3 mo.	0.07	1.96	ND	3+	4+	4.6	±	3.1	1.58	0
	6 mo.	0.14	1.92	ND	0	1+	4.6	0	3.2	ND	ND
3	2	0.32	1.60	ND	3+	4+	2.7	1+	4.5	10.9	+
	2 mo.	0.06	1.50	ND	0	2+	3.6	±	4.0	1.32	0
4	4	0.99	3.10	58	ND	ND	1.9	ND	6.3	0.65	+
	8	0.26	0.68	20	3+	ND	3.1	ND	9.3	0.38	0
6	3	0.04	0.36	3.6	1+	3+	5.9	0	5.2	0.21	0
7	3	0.21	0.72	16.8	0	ND	5.9	1+	4.0	0.15	0
	8	0.10	0.52	3.4	0	0	5.3	2+	3.4	1.42	0
10	0	0.25	0.80	4.2	0	0	2.6	0	4.5	0.18	0
13	3	Less than	0.8	ND	0		1.3	ND	8.7	ND	ND
14	7	Less than	0.8	ND	0		1.5	ND	6.1	ND	ND
15	3	Less than	0.8	ND	0		1.2	ND	3.5	ND	ND
16	2	0.8	1.8	ND	ND		ND	ND	3.1	ND	ND
	7	0.8	1.1	ND	ND		ND	ND	2.4	ND	ND

*Normal values for liver function tests: Direct bilirubin, <0.22 mg./100cc.; total bilirubin, <1.3 mg./100cc.; BSP (45 min.), <6%; cephalin flocculation, <1+/2+ (24/48 hr.); thymol turbidity, <5.0 units; alkaline phosphatase, <8.0 units; urine urobilinogen, <1.3 units; urine bile, 0. ND indicates not done.

and increase in urinary urobilinogen. The persistence of bilirubinemia two to six months after discharge from the hospital suggests the possibility of some low-grade hemolytic process, perhaps familial. Neither was anemic, no abnormal erythrocytes were seen in stained smears of peripheral blood, and a sickle-cell preparation was negative in Case 2. No electrophoretic analysis for abnormal hemoglobins was carried out in either case. In Case 4, there was elevation of serum bilirubin, bilirubinuria, and striking sulfobromophthalein retention. Serum bilirubin returned to normal promptly, and, at the time of discharge, there was improvement in sulfobromophthalein clearance, although the serum alkaline phosphatase had risen and the cephalin flocculation test was abnormal. Sulfobromophthalein retention was prominent in Cases 1 and 7 also. In each of the nine cases, there was return of liver function tests toward normal as orchitis subsided.

TABLE 4.—*Summary of Liver Function Tests in Eleven Cases of Mumps Orchitis*

Examination	Admission No. Normal	Admission No. Abnormal	Discharge No. Normal	Discharge No. Abnormal
Serum bilirubin	8	3	4	1
BSP	2	4	1	1
Cephalin flocculation	4	4	3	1
Thymol turbidity	8	2	5	1
Alkaline phosphatase	9	2	5	1
Urine urobilinogen	5	2	4	0
Urine bile	5	2	5	0

In none of the patients was icterus clinically apparent, and there was no correlation between the results of laboratory tests of liver function and the severity of illness or response to corticosteroid therapy.

Effect of Adrenocortical Hormones

Twenty-one patients were given cortisone, one received repository corticotropin injection intramuscularly, and one was treated with prednisone (Meticorten). The dosages for individual patients are shown in Table 1. With the exception of corticotropin (ACTH), drugs were given orally unless nausea made it necessary to use the parenteral route; in none of the patients was this done after the first day of treatment. The daily dose and the duration of treatment varied considerably. Generally, the most satisfactory program appeared to be an initial dose of 300 mg. of cortisone followed by 200 mg. daily, with raipd tapering of hormone as soon as clinical response allowed. In the entire study, duration of treatment ranged from 3 to 18 days and total dosage from 500 to 4100 mg. This latter amount was used in Case 10, described below. The average dosage of cortisone was 1100 mg. over a period of seven days.

Response to therapy was evaluated primarily on the basis of relief of testicular swelling, pain, and tenderness. Improvement

in general well-being and subsidence of fever were also considered because, with the exception of three patients with concomitant pancreatitis and one (Case 10) who developed orchitis while on cortisone therapy for severe parotitis, the rapidity of response of the orchitis to administration of the hormones was paralleled by the speed of defervescence and relief of systemic discomfort and malaise. Candel [23] has pointed out this correlation between severity of testicular inflammation and height of fever in mumps orchitis.

Local Manifestations.—The objective and subjective relief experienced by 22 of the 23 patients given corticosteroids was striking. In 14 patients, amelioration of pain and decrease in swelling during the first 24 hours of treatment were dramatic, and within 48 hours none of the 22 had more than slight testicular tenderness on palpation. Tenderness of the epididymis persisted for a few more days in several instances, but discomfort was minimal.

Serum amylase determinations are often abnormal during parotid involvement in mumps.[24] In three patients in whom parotitis had subsided before admission, abdominal pain and nausea coupled with the finding of elevation of serum amylase led to a diagnosis of pancreatitis. In these patients, relief of testicular pain was prompt; however, all three remained ill for several more days with abdominal discomfort and low-grade fever.

Fever.—The mean duration of fever after institution of hormone therapy in the 23 cases was 36 hours. In 12 patients, defer-

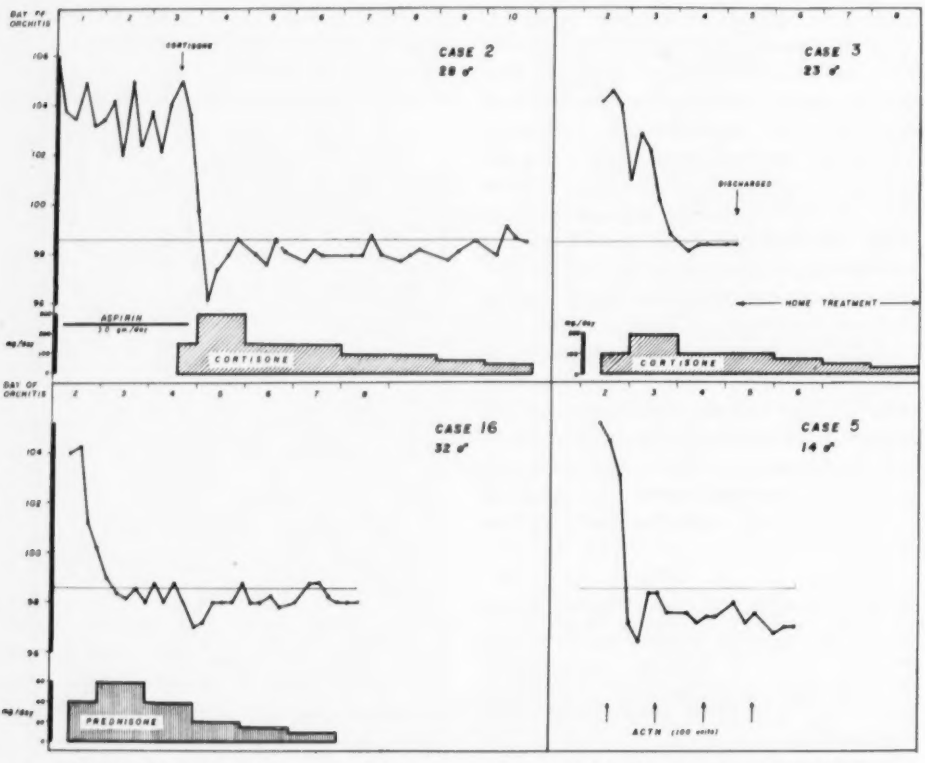

Fig. 1.—Examples of dramatic defervescence after administration of adrenal steroids in mumps orchitis. Note failure of large doses of acetylsalicylic acid to control fever in Case 2 and feasibility of home treatment in Case 3. Case 5 responded to corticotropin (ACTH), and Case 16, to prednisone.

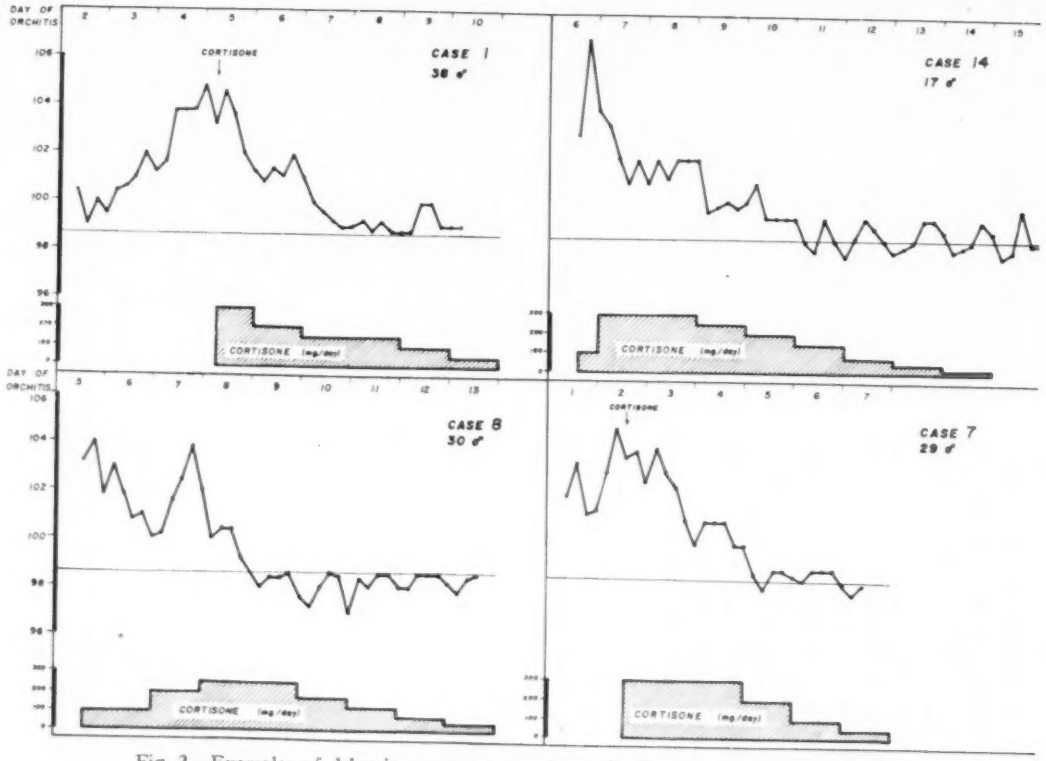

Fig. 2.—Examples of delay in response to cortisone. In Case 1, treatment was begun relatively late in the disease. Case 14 had pancreatitis in addition to orchitis and continued to have low-grade fever and abdominal pain despite amelioration of testicular pain and swelling. In Case 8, the initial dosage of hormone was probably inadequate.

vescence occurred in less than 24 hours, 5 required 24-48 hours for return to normal temperature, and in only 1 instance did fever persist for longer than 72 hours. Figure 1 illustrates some examples of the dramatic relief of fever by corticosteroids in mumps orchitis. It is noteworthy that fever had persisted in a number of patients despite administration of acetylsalicylic acid but fell by crisis after institution of hormonal therapy. This resistance to acetylsalicylic acid of fever in mumps orchitis has been noted before.[25] Examination of case records of patients in whom defervescence was slower, some examples of which are illustrated in Figure 2, indicated that inadequate initial dosage of steroid, long duration of orchitis before treatment, and the presence of complicating pancreatitis were factors that may have contributed to delay in response.

Other Effects of Corticosteroids.—As mentioned above, three patients with pancreatitis (Cases 14, 15, and 20) continued to have upper abdominal pain and nausea after testicular swelling had subsided. Furthermore, defervescence in these patients required 104, 60, and 54 hours, respectively. While it cannot be said that cortisone had no influence upon the duration of pancreatic disease, it is clear that its effect upon pancreatitis was not one of dramatic amelioration.

In none of the eight patients with cerebrospinal fluid pleocytosis was the administration of cortisone followed by any evidence of aggravation of this process. Headache subsided in all, and no signs of meningeal irritation appeared.

In one patient who had been given cortisone for parotitis alone, orchitis developed 48 hours after institution of hormonal therapy. This case will be presented in some detail.

Case 10. (Fig. 3).—A 28-year-old medical student noted headache, malaise, chilliness, anorexia, and lethargy followed 24 hours later by bilateral parotid swelling. He was hospitalized one day later.

Admission temperature was 99.6 F, and except for bilateral tender swellings of the parotid and submaxillary salivary glands, no abnormalities were found. The gonads were normal. Leukocyte count was 11,050 per cubic millimeter, and serum amylase, 416 units.

During the next three days, the patient became febrile, and his malaise increased. The institution of cortisone therapy on the fourth hospital day was

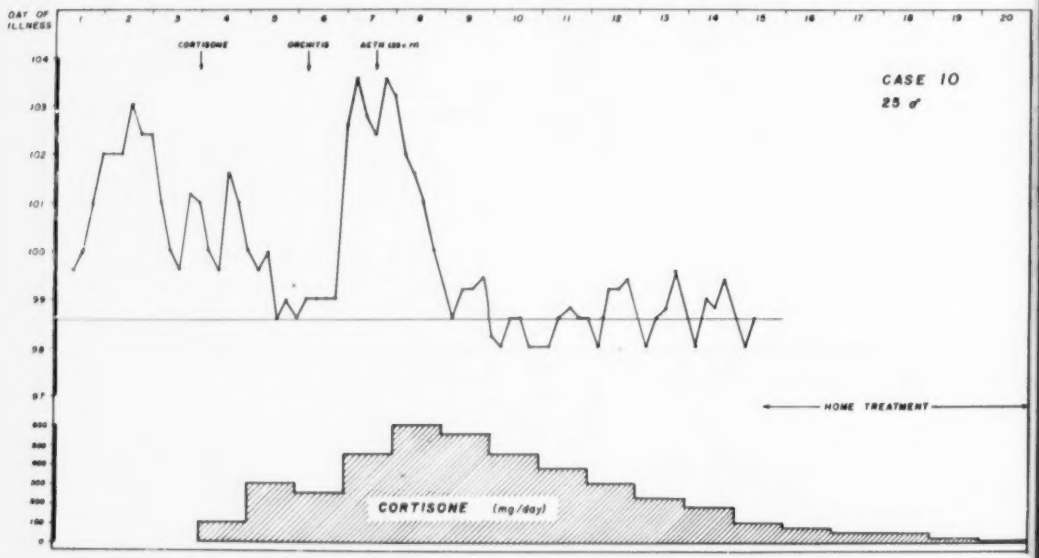

Fig. 3.—Development of orchitis in a patient already receiving cortisone for parotitis.

followed by subsidence of fever and improvement in general well-being and appetite. However, 48 hours later, after having received a total of 400 mg. of cortisone by mouth, the patient suddenly developed painful swelling of the right testis, his temperature rose from 99 to 103 F within eight hours, and he became acutely ill. During the ensuing 48 hours he received 1050 mg. of cortisone orally and 25 units of corticotropin intravenously. On this regimen, pain and fever subsided and steroid dosage was reduced gradually over a period of seven days without recurrence. Definite atrophy of the right testicle was present two months after discharge from the hospital.

There were no untoward effects of steroid therapy upon blood pressure, carbohydrate metabolism, or gastrointestinal function, and no mental aberrations were noted in any patient. In the following case, however, administration of cortisone may have masked the symptoms of coexisting brucellosis.

CASE 9.—A 22-year-old employee of a meat-packing plant developed fever and right parotid swelling. During the next few days, left parotitis appeared, and on the sixth day of illness, pain and swelling of the right testicle began. He was admitted on the seventh day of illness, with fever, headache, and severe testicular pain. He had also complained of excruciating pain in the region of the lumbar spine during the week before hospitalization.

Temperature was 104.3 F. There was obvious left parotitis and right orchitis. No lymphadenopathy was found, and the spleen was not palpable. There was no tenderness over the spine, and neurologic examination was normal. Leukocytes numbered 3400 per cubic millimeter, with a normal differential count. Mumps complement fixation reaction was negative on admission, but serum drawn two weeks later was positive in a titer of 1:64.

The patient was given 300 mg. of cortisone initially and received a total of 750 mg. during a five-day period. He was afebrile and asymptomatic within 24 hours after institution of hormone therapy and was discharged on the seventh day.

Because the patient was an employee at a packing plant from which a number of cases of brucellosis had been reported in recent years, serum agglutinins for Brucella were measured and found to be present in a titer of 1:320. Before discharge, therefore, blood and bone marrow cultures were planted; Brucella melitensis grew from both. Although he had continued without symptoms, the patient was readmitted 10 days after discharge and treated with chlortetracycline (Aureomycin) and streptomycin for two weeks. He has remained healthy and asymptomatic. Subsequent cultures have been sterile.

This patient had been asymptomatic until the onset of parotitis and remained asymptomatic after cortisone treatment and discharge from the hospital, despite the presence of B. melitensis in blood and marrow cultures. Whether the brief course of corticosteroids actually suppressed or delayed the appearance of symptoms of brucellosis in this patient cannot, of course, be stated. However, this case emphasizes that the ability of cortisone to relieve discomfort in many types of disease can mask important symptoms and confuse diagnosis.

Follow-up Studies.—Ten of the twenty-three patients were not seen again after discharge from the hospital; one of these, however, fathered two children during the three years after bilateral orchitis.

Of the 13 patients in whom follow-up examinations were carried out one to six months after discharge from the hospital, eight showed no residual testicular atrophy. One of this group was a patient who had had azoospermia at the time of the acute illness but showed no atrophy of the testes six months later (sperm count was not repeated at that time). Four patients showed definite atrophic changes. The last patient, in whom bilateral orchitis had occurred, was followed at intervals for one year. Although both testes were somewhat small, they were thought by all observers to be normal in consistency, and no clear-cut atrophy could be demonstrated. However, sperm counts carried out 6 months and 12 months after recovery revealed no sperm. Libido was unaffected, and the ejaculate was normal in volume.

Three of the five patients who developed testicular atrophy or azoospermia required more than 36 hours for defervescence on steroids. All of the eight without residual had defervesced in less than 36 hours; indeed, the mean duration of fever in this group was only 22 hours.

Although these data are scanty, they suggest that atrophy is less likely to occur when orchitis shows a good initial response to

administration of corticosteroids. This is not unreasonable if atrophy is a result of swelling and pressure on the testicle within the tunica albuginea.

Comment

Manifestations of Mumps Orchitis.—The 23 patients reported here represent selected cases. With one exception (Case 10) the presenting complaint was testicular pain, and illness was adjudged to be of sufficient severity to warrant admission to hospitals in which it is not customary to care for patients with uncomplicated mumps.

The clinical course of disease in these patients corresponded with previous descriptions of orchitis. Parotitis preceded the development of this complication by 1 to 10 days, falling well within the range reported by Eagles.[4] This author reported 628 cases of orchitis in which the onset of testicular involvement ranged from 14 days before to 25 days after parotitis, averaging 4.5 days after salivary gland swelling. Candel[23] studied 68 cases of orchitis and found that the onset of testicular disease occurred during the first week after parotid involvement in 66%, the second week in 25%, and the third week in 9%. One of our patients (Case 17) had no salivary adenitis at any time. This has been reported many times in the course of epidemics and is well reviewed in Candel's paper.

The occurrence of shaking chills at the onset of orchitis is common. Four patients in the present group of 23 and 17 of Candel's 68 cases had at least one true rigor. This type of onset, along with the striking polymorphonuclear leukocytosis that often occurs, emphasizes Wesselhoeft's statement[22] that testicular involvement in mumps behaves clinically like a localized suppurative process.

Comparison of the clinical findings in these 23 sporadic cases of mumps orchitis with groups of consecutive cases in epidemics suggests that they were of more than average severity. In nine (39%) both testicles were involved. Bilateral disease occurred in 12 (18.2%) of the 66 cases reported by Candel,[23] 63 (14.8%) of 427 cases reviewed by Eagles,[4] and 52 (10.6%) of 494 cases seen by McGuiness and Gall.[1] Candel's careful study showed clearly that the best clinical indication of severity of orchitis is the height of the febrile response. In his patients, the average maximum temperature was 101.4 F, with a mode of about 103 F. In the present series, the mean peak was 104.4 F, with a mode of about 104.6 F. In only 12 of Candel's 66 cases did fever exceed 104.2 F, while 16 of the 23 patients in the present study had elevations in this range. The average leukocyte count in these cases was 12,400 per cubic millimeter, considerably higher than the 7700 reported by McGuiness and Gall as the mean in 164 cases.[1]

Response to Corticosteroids.—Occasional suggestions that adrenocortical hormones might be useful in mumps orchitis have appeared.[25-28] The only detailed report to date is that of Solem,[29] who treated six patients by daily intramuscular injection of 100 units of a depot preparation of corticotropin. Four patients responded to a single dose with dramatic subjective relief and defervescence within 24 hours. A fifth relapsed twice after initial improvement, probably as a result of inadequate dosage. The last patient had pancreatitis in addition to orchitis, and despite prompt subsidence of gonadal pain and swelling, abdominal discomfort persisted. A similar course of events was observed in the three patients with concomitant pancreatitis in the present study (Cases 14, 15, and 20) in whom, despite amelioration of orchitis, abdominal pain and low-grade fever continued for several days after administration of cortisone. A recent report of beneficial effects of cortisone in a single case of mumps pancreatitis[30] is difficult to evaluate. In addition to pancreatitis, the patient had orchitis and, at one point, was stuporous. No spinal fluid examination was reported, and it is not at all clear from the data provided that pan-

creatitis was responsible for the patient's stormy course.

The variability of the clinical course of epididymo-orchitis in mumps makes evaluation of any therapeutic regimen difficult. In 1951, Candel [23] reviewed the manifestations of this disorder, with special consideration of the natural history of the disease as a basis for judging the efficacy of various methods of treatment. In particular, the relatively short duration of fever in untreated orchitis, the defervescence by crisis in 50% of the cases, and the progression of testicular atrophy over a period of months or years were emphasized.

This study of the effect of corticosteroids upon mumps orchitis was carried out without the use of alternate or randomly selected untreated controls. However, if the composite natural history of untreated orchitis in consecutive epidemic cases is used as a basis for evaluation of the results of steroid treatment, it is apparent that the hormones exerted a beneficial effect.

According to Candel, the average duration of fever in 62 consecutive cases was 4.3 days, with 22.5% of cases febrile 3 days or less, 54.8% for 4 days or less, and 83.8% for 5 days or less. In another series of 628 consecutive cases of orchitis, fever persisted for an average of 3.6 days,[4] and McGuiness and Gall reported a mean of 4.2 days for the febrile period. Furthermore, termination of fever in 55 untreated patients occurred by crisis in 28 and by lysis within four days in the remainder. Omitting the three patients with concomitant pancreatitis, the results of adrenal steroid therapy in 20 patients with epididymo-orchitis in the present study show a mean duration of fever before institution of treatment of 2.2 days and 1.1 day after initiation of therapy, a total duration of 3.3 days. Fever persisted for three days or less in 8 patients (40%) and four days or less in 14 (70%) and subsided by crisis in 12 (60%) patients given cortisone. The average time required for defervescence in all patients was 26 hours, as opposed to 44 hours derived from Candel's data on subsidence of fever in 55 untreated cases.

The incomplete nature of the follow-up examinations in patients treated with adrenal hormones allows no dogmatic statement as to the effect of this therapy on the incidence of testicular atrophy. However, it was the general impression that patients who responded by crisis were less likely to show atrophic changes during the few months after acute disease and that prompt administration of an initial dose of 300 mg. of cortisone (or its equivalent) was most important in achieving this result.

These attempts to compare, in a quantitative fashion, the clinical course of unrelated groups of patients, studied by different observers under different circumstances, are not offered as a substitute for further observations in a single series of patients selected at random and controlled by appropriate placebo methods. However, the clinical response to corticosteroids in these 23 cases of severe epididymo-orchitis was so uniformly satisfactory in terms of relief of pain and systemic discomfort that the authors regard these drugs as the treatment of choice. Indeed, the symptomatic management of this painful complication of mumps is no longer regarded as a problem. The regimens that have been accorded enthusiastic praise in the therapy of epididymo-orchitis in mumps, only to be discarded after more critical evaluation, constitute an impressive list. The results obtained with corticosteroids in the treatment of this group of cases seen sporadically during the past few years have been so striking that these hormones deserve wider trial in the treatment of orchitis. Evaluation of their usefulness in prevention of this complication in the course of epidemic parotitis would also be worth while.

Liver Function in Mumps.—Nine of the eleven cases in which liver function tests were performed showed definite abnormalities. In five instances, these were severe enough to cause concern, although in all cases, evidences of derangement of hepatic

function returned toward normal as the acute illness subsided. There is little documentation of hepatic involvement in mumps. A recent report by Hloucal and his associates [31] describes hepatomegaly and icterus in a 13-year-old girl with mumps parotitis and oophoritis. Her serum bilirubin was 3.2 mg. per 100 cc., and there was increased urinary excretion of urobilinogen. Two cases of icterus and hepatomegaly following mumps at intervals of one week and five weeks were mentioned in a letter to the editor of the *Lancet*.[32] These, of course, could well have been examples of unrelated viral hepatitis.

It is because the literature contains so little mention of hepatic involvement in mumps that the admittedly incomplete findings in the present study have been presented in detail. Further systematic investigations of this feature of the disease should be carried out.

Summary

The administration of cortisone, prednisone, or corticotropin to 23 patients with severe mumps orchitis was followed by rapid defervescence and reduction of testicular swelling and pain. No untoward effects of these hormones upon the course of the infection were noted. The desirability of wider clinical trial of this type of treatment is pointed out. The occurrence of hepatic dysfunction of varying degree in several patients in this group is discussed in relation to the paucity of published data on involvement of the liver in mumps.

Addendum

Since this paper was submitted for publication, Stenberg and Berry (*U. S. Armed Forces Med. J.* 7:1414, 1956) have reported experience with cortisone in the treatment of 14 cases of mumps orchitis. Although adrenal hormones were beneficial in their cases of severe orchitis, they were ineffective in preventing this complication in several patients in whom treatment was begun during the stage of parotitis. Risman (*J. A. M. A.* 162:875, 1956) described prompt relief of pain when cortisone was given to five patients with mumps orchitis but little effect of the hormone on testicular swelling or fever. Subsequent mild involvement of the contralateral gonad occurred in three patients while still on therapy. Rapid tapering of the drug and low dosage may account for these results. Klemola and Somer (*Nord. med.* 56:1128, 1956) studied 105 cases of mumps orchitis, 53 treated with placebo injections, 41 with depot corticotropin intramuscularly for four days (40 units, 20 units, 20 units, and 10 units, respectively), and 11 with intramuscular cortisone on the following daily schedule: 100 mg.×2, 100 mg.×2, 100 mg. and 50 mg., 100 mg.×1, 75 mg.×1, 50 mg.×1, and 25 mg.×1. Although these observers reported no significant difference between the groups in duration of fever or symptoms, the relatively low dosage of corticotropin (ACTH) and the use of the parenteral route for administration of cortisone make it difficult to draw definite conclusions. In the experience of the present authors, best results have followed an initial oral dose of 300 mg. of cortisone or its equivalent.

Warren (A. M. A. Arch. Int. Med. 98: 525, 1956) described tender hepatomegaly, icterus, and abnormalities in liver function in a patient with mumps orchitis. This case report emphasizes the need for further observations on the incidence and significance of hepatic involvement in mumps.

Dr. Paul B. Beeson gave permission to include cases observed in New Haven, and Dr. Eugene B. Ferris gave permission to include cases seen in Atlanta.

The Johns Hopkins Hospital.

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The Thyroid-Stimulating Hormone (TSH) Test

An Aid to the Differential Diagnosis of Nontoxic Disease of the Thyroid

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The thyroidal radioactive iodine (I^{131}) uptake alone has only been of limited value as a diagnostic aid in the differential diagnosis of nontoxic thyroid disease. However, measurement of the thyroidal uptake of radioactive iodine (I^{131})* before and after the administration of thyroid-stimulating hormone (thyrotropin) has greatly enhanced the usefulness of this diagnostic tool. The purpose of this paper is to describe the results of the thyroid-stimulating hormone (TSH) test in patients having various nontoxic thyroid diseases with and without goiter and patients with normal thyroid function.

Review of the Literature

Stanley and Astwood [1] first demonstrated that in patients with normal thyroid function (euthyroidism) a single injection of TSH caused a significant increase in the rate of thyroidal uptake of I^{131} at the end of 8 hours which reached its peak at the end of 24 hours. They noted that the duration of the increased rate of uptake usually was about four days. In addition, they demonstrated that a significant increase in the radioiodine uptake also occurred in euthyroid patients who were taking desiccated thyroid. These observations have been confirmed by others.[2,3]

Werner and associates,[2] as well as Querido and Stanbury,[4] first reported and others [5,6] first confirmed that in patients with primary hypothyroidism, repeated injections of TSH resulted in no increase in I^{131} uptake, while in patients with thyroid failure secondary to anterior pituitary failure, such injections usually caused a significant increase in uptake.

Perlmutter and associates [3] and Jefferies and associates [7] reported that a single intramuscular injection of a small dose of TSH (4 U. S. P. units) produced the same results in euthyroidism and primary hypothyroidism as did repeated injections of larger doses. Jefferies and associates also observed that I^{131} uptake could be accurately measured over a shorter period of time (3 hours) than the 24-hour interval that had been used previously. Bishopric and associates [8] confirmed these observations.

Levy and associates [9] reported that TSH did not increase the I^{131} uptake in hypothyroid children whom they regarded as having congenital goiter and in one adult; but pathologic studies were not performed in those patients. Skillern and associates [10] showed that a single injection of 4 units of TSH did not significantly increase the rate of I^{131} uptake in 23 patients with pathologically proved struma lymphomatosa in contrast to the significant increase observed in 18 patients with nontoxic adenomatous (nodular) goiter. Parmley and Hellwig [11] first suggested that in patients with struma lymphomatosa there may be an increase in production of endogenous TSH by the pituitary gland, causing hyperplasia of the

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* The radioactive material used in this investigation was supplied by the Abbott Laboratories on authorization from the Isotopes Division, U. S. Atomic Energy Commission, Oak Ridge, Tenn.

thyroid follicles, which could be suppressed by thyroxine. Gribetz and associates [12] suggested that a deficiency of thyroxine production might be the cause of this increased TSH production.

Robbins and associates [13] reported that repeated large injections of TSH significantly increased the I^{131} uptake in most patients with subacute nonsuppurative thyroiditis. In contrast, Skillern and associates [14] reported that no significant increase in I^{131} uptake occurred in 10 of 12 such patients when a 4 unit dose of TSH was given.

Werner and associates [15] found that the TSH did not significantly increase the I^{131} uptake in six of eight euthyroid patients with untreated Graves' disease with exophthalmos. These workers [15] advocated the use of the TSH test as an aid in differentiating the euthyroid patient with unilateral or bilateral exophthalmos due to Graves' disease from the patient with exophthalmos due to other causes. Werner and associates,[16] Kelly and associates,[17] and Martin and Stanbury [18] have reported abnormal TSH tests in some euthyroid patients with I^{131}-treated Graves' disease. Kelly and associates [17] also observed abnormal TSH tests in euthyroid patients with surgically treated Graves' disease.

Methods and Materials

The procedure for the TSH test as described by Jefferies and associates [7] was followed, except that I^{131} uptakes were measured after six instead of after three hours in order to be sure of more complete absorption of I^{131} from the gastrointestinal tract and to demonstrate a more definitive difference in the rate of I^{131} uptake. On the first day a tracer dose of approximately 20 μc of I^{131} in liquid or capsule form was given. (Most of the patients were fasting, and all had not eaten for at least three hours before the I^{131} was administered.) A six-hour I^{131} uptake over the thyroid gland was measured with a scintillation counter. Then, a single intramuscular injection of 4 U. S. P. units of thyrotropin in freshly prepared saline solution was given. On the next day, 24 hours after the administration of the first tracer, residual activity in the thyroid gland was measured, and a second tracer, containing approximately 20 to 50 μc of I^{131} was administered under the same circumstances as those for the first tracer. The I^{131} uptake over the thyroid was measured six hours later, and the residual 24-hour radioactivity from the first tracer was subtracted from the measurement of the second tracer. The effect of the TSH was evaluated by comparing the six-hour I^{131} uptakes before and after the administration of TSH.

No organic or inorganic iodine had been recently given to any of the patients in this study because it inhibits the I^{131} uptake by the thyroid gland and the response to a small dose of TSH.

The various thyroid diseases studied are listed in the Table. Also TSH tests were done on normal control patients without thyroid disease who were or were not taking desiccated thyroid.

Results of TSH Tests in Various Nontoxic Thyroid States

	No. Patients Tested	TSH Tests	
		Normal	Abnormal
Untreated euthyroid patients without thyroid disease	32	32	0
Untreated primary hypothyroidism	17	0	17
Anterior pituitary failure	11	7	4
Treated* euthyroid patients without thyroid disease	29	25	4
Treated* primary hypothyroidism	11	0	11
Treated* struma lymphomatosa	11	1	10
Euthyroid patients with			
A. Untreated Graves' disease	6	4	2
B. Treated Graves' disease			
Radioactive iodine	7	6	1
Surgery	5	0	5
Untreated struma lymphomatosa	31	1	30
Untreated nontoxic adenomatous goiter	31	31	0
Carcinoma of thyroid	6	6	0
Subacute nonsuppurative thyroiditis	14	2	12

*Desiccated thyroid.

The diagnosis of primary hypothyroidism was substantiated by obvious symptoms and signs, including myxedematous facies, low basal metabolic rates, and high serum cholesterol values. These findings all were reversed to normal by the administration of desiccated thyroid. The diagnosis of anterior pituitary failure was substantiated by clinical findings of deficiency of other endocrine glands, usually the presence of pituitary tumor, and tests of other endocrine function. The diagnosis of struma lymphomatosa was proved by needle biopsy in 25 patients and in 6 other adult patients by the presence of both clinical and laboratory evidence of hypothyroidism and diffuse goiter. The diagnosis of nontoxic adenomatous goiter was confirmed by surgical removal in 12 of 31 patients, as was the diagnosis of carcinoma of the thyroid in all patients. The diagnosis of subacute thy-

roiditis was made in 12 of 14 patients on the basis of obvious typical clinical and laboratory findings, but needle biopsy was done in the other two patients.

Results

Normal and Abnormal TSH Test.—The thyroid-stimulating hormone (TSH) test was regarded as normal when the radioiodine uptake after TSH was significantly greater than that before TSH. If the initial I^{131} uptake was low (10% or less), an increase of 100% or more of the initial uptake was a significant increase. If the initial I^{131} uptake was normal (11% to 50%), an increase of 50% or more of the initial uptake was a significant increase. If the initial I^{131} uptake was high (above 50%), an increase of 15 points or more in I^{131} uptake was regarded as a significant increase. The failure of TSH to cause a significant increase in I^{131} uptake was called an abnormal test. The number of patients tested and the results of the TSH test in normal patients and patients with various nontoxic thyroid disease are summarized in the Table.

Euthyroid Patients.—The TSH test was normal in 32 of 32 nongoitrous patients with normal thyroid function who were not taking desiccated thyroid (Fig. 1). The sharp increase in I^{131} uptake after the administration of 4 units of TSH rules out primary hypothyroidism.

Patients with Primary Hypothyroidism.—The I^{131} uptake is usually, but not always, 10% or less in patients with untreated primary hypothyroidism. The TSH test was abnormal in all 17 patients with untreated primary thyroid failure (Fig. 1). In 13 of the patients the failure was spontaneous, in 2 it followed I^{131} treatment, and in 2 it occurred after surgical treatment for Graves' disease.

Patients With Anterior Pituitary Failure Without Clinical Hypothyroidism.—In 9 of the 11 patients in this group, the I^{131} uptakes were above 10%, in contrast to the lower values usually observed in those having primary hypothyroidism. The TSH test was normal in 7 of 11 patients with anterior pituitary failure. Even when larger repeated doses of TSH were administered to one of these patients who had had an abnormal test with the small dose, no significant increase in I^{131} uptake occurred (Fig. 1). In one other patient 10 units of TSH raised the I^{131} uptake only from 20% to 23%, but another 10 units increased it to 49%.

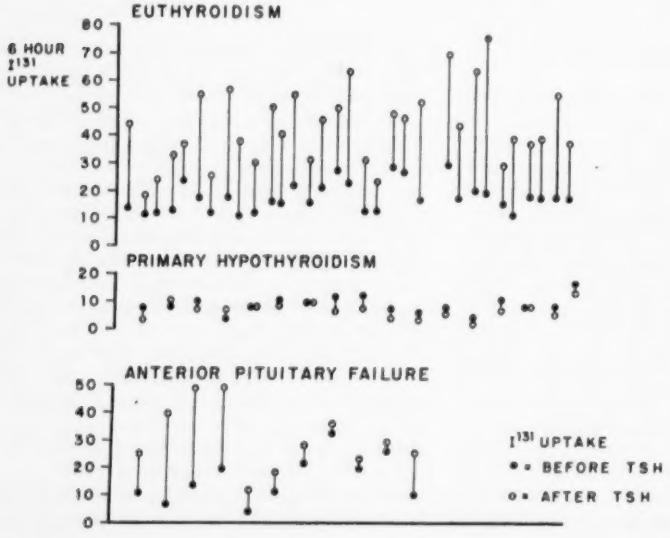

Fig. 1.—Response of radioiodine uptake to thyroid-stimulating hormone in patients with normal thyroid function, primary hypothyroidism, and anterior pituitary failure without clinical hypothyroidism.

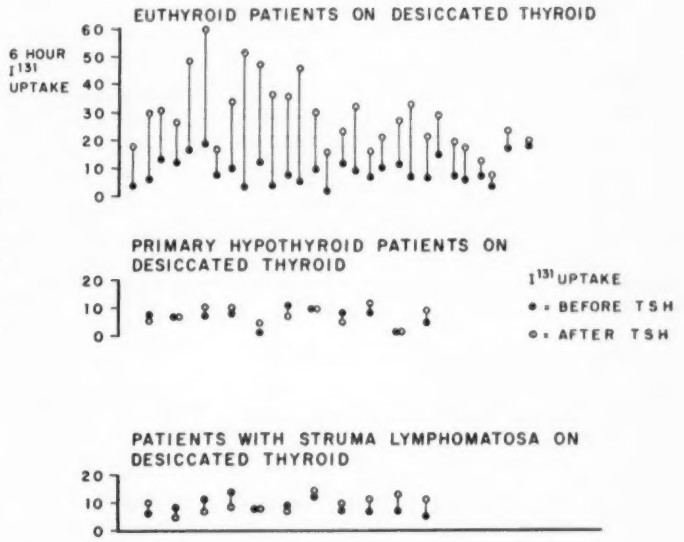

Fig. 2.—Response of radioiodine uptake to thyroid-stimulating hormone in patients with normal thyroid function, primary hypothyroidism, and struma lymphomatosa taking desiccated thyroid.

Patients with Euthyroidism or Primary Hypothyroidism (Taking Desiccated Thyroid).—The TSH test was normal in 25 of 29 euthyroid patients who were taking desiccated thyroid and abnormal in all 11 patients with primary hypothyroidism who also were taking desiccated thyroid (Fig. 2).

Most of the euthyroid patients with a normal TSH test had taken 1½ to 3 grains (97 to 194 mg.) of desiccated thyroid for one to four years. Three such patients with a normal TSH test had taken 1, 1½, and 2 grains (65, 97, and 130 mg.) of desiccated thyroid for 9, 14, and 25 years. The four euthyroid patients with an abnormal TSH test had taken 1½, 2, 3, and 5 grains (97, 130, 194, and 324 mg.) of desiccated thyroid for 5, 11, 17, and 12 years, respectively. The initial six-hour I^{131} uptakes in two of these four patients were in the normal range (17% and 18%), which per se favored the diagnosis of euthyroidism. The patients were still euthyroid two months after stopping the desiccated thyroid. In these four euthyroid patients the administration of moderate to large doses of desiccated thyroid over a prolonged period probably produced pronounced physiologic atrophy of the thyroid cells that were then unable to respond to a single small or even moderate dose of TSH. One of these patients had an abnormal TSH test with I^{131} uptakes of 7% and 4% before and after TSH, respectively. He had been taking 5 grains of desiccated thyroid daily for 12 years. After two days of treatment with 4 units of TSH, the I^{131} uptake did not increase. Two months after stopping the desiccated thyroid, the six-hour I^{131} uptakes before and after 4 units of TSH were 10% and 7%, respectively. The patient was clinically euthyroid. Seven months later the patient still was clinically euthyroid, but six-hour I^{131} uptakes were 14% and 20% before and after 4 units of TSH, respectively, and the basal metabolic rate was −19%.

Euthyroid Patients with Untreated and Treated Graves' Disease.—The TSH test was abnormal in only two of six patients having untreated Graves' disease with unilateral or bilateral exophthalmos without hyperthyroidism. The test was normal in six of seven euthyroid patients after treatment of Graves' disease with radioiodine, and abnormal in five of five patients after surgical treatment (Fig. 1). Two of these patients with abnormal TSH tests had had surgery 16 and 20 years previously.

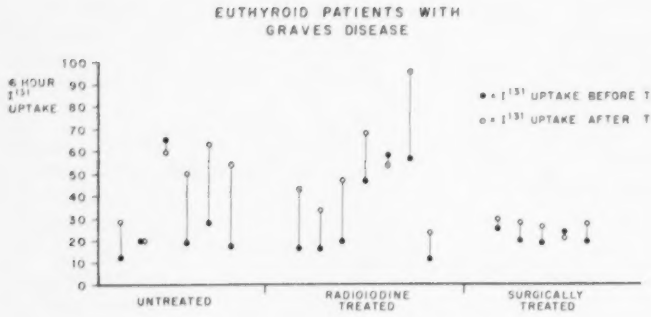

Fig. 3.—Response of radioiodine uptake to thyroid-stimulating hormone in euthyroid patients with untreated Graves' disease and postradioiodine and surgically treated Graves' disease.

Patients with Struma Lymphomatosa.—The I^{131} uptake ranges from low to high in patients with struma lymphomatosa (Fig. 3). Regardless of the value of the initial I^{131} uptake, the administration of 4 units of TSH did not produce a significant increase in I^{131} uptake in 30 of 31 patients with struma lymphomatosa (Fig. 3). A larger amount of TSH will produce a significant increase in I^{131} uptake in some patients with struma lymphomatosa.

The one patient with a normal six-hour TSH test in which the I^{131} uptake increased from 18% to 40% had only enlargement of the midline pyramidal lobe. The lateral lobes were firm but not enlarged. The diagnosis of struma lymphomatosa was confirmed by surgical removal of only the pyramidal lobe. One month later the six-hour TSH test was repeated and was found to be abnormal, increasing only from 19% to 24%. It is possible that the original normal TSH test was due to technical error, but we believe that it is possible that a sufficient number of thyroid cells in the lateral lobes had not yet undergone failure and responded to TSH.

Patients with Nontoxic Adenomatous (Nodular) Goiter.—In contrast, the TSH test was normal in 31 of 31 patients with nontoxic adenomatous goiter (Fig. 2). If the initial uptake is high in a nontoxic patient with a hyperfunctioning nodule, an occasional equivocal result may be obtained, especially if the 24-hour TSH test is done.

Patients with Struma Lymphomatosa (Taking Desiccated Thyroid).—The TSH test (4 units of TSH) was abnormal in 10

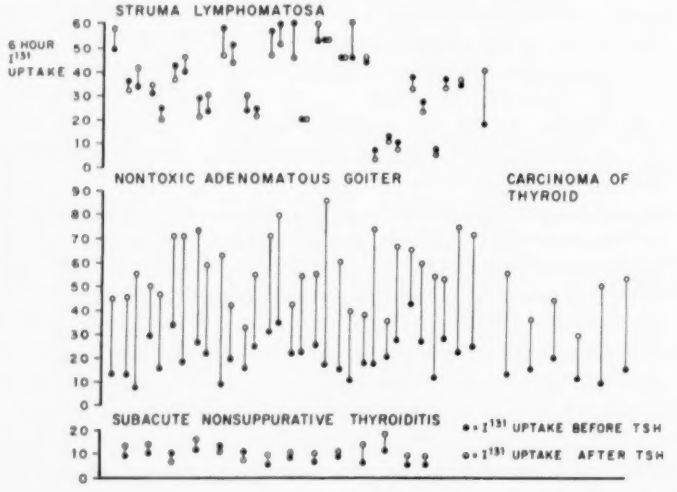

Fig. 4.—Response of radioiodine uptake to thyroid-stimulating hormone in patients with struma lymphomatosa, nontoxic adenomatous goiter, carcinoma of the thyroid, and subacute thyroiditis.

of 11 patients with struma lymphomatosa who had been taking 3 grains of desiccated thyroid daily (Fig. 4). An increased dose of TSH (10 to 20 units) resulted in normal TSH tests in two such patients.

Patients with Carcinoma of the Thyroid and Subacute Thyroiditis.—The TSH test was normal in three patients with solitary nodule due to papillary carcinoma, one patient with recurrent papillary carcinoma, one patient with diffuse goiter due to angioinvasive carcinoma, and one patient with undifferentiated adenocarcinoma (Fig. 4). The TSH test was abnormal in 12 of 14 patients with subacute nonsuppurative thyroiditis (Fig. 4).

Comment

The availability of a purified preparation of thyrotropin has greatly increased the usefulness of the radioiodine tracer as an aid in differentiating various nontoxic thyroid diseases with and without goiter. The observation that only a single small inexpensive intramuscular injection of TSH is required, instead of several repeated doses, has made the TSH test even more practical.[3,7,8,10] When the single-dose TSH test is used, it can be performed in two days, and only two simple measurements of radioiodine uptake over the thyroid are necessary. We agree with Jefferies and associates [7] that the only undesirable side-effect has been an occasional local discomfort at the site of injection when only a small dose of thyrotropin is given. The administration of inorganic or organic iodine will result in an inaccurate test. The results of the TSH test, like any thyroid-function test, should be correlated with clinical findings, basal metabolic rate, serum cholesterol, and other pertinent laboratory findings. We have found it impractical and unnecessary to measure protein-bound iodine values before and after the administration of TSH, as suggested by others,[3,7] to help differentiate the euthyroid patient from one with primary hypothyroidism.

The results of our studies further indicate that the TSH test is an important aid in differentiating euthyroidism from mild to moderate primary hypothyroidism. However, we believe that the TSH test need not be performed when the diagnosis of primary hypothyroidism has been substantiated by obvious clinical findings, a low basal metabolic rate, and an elevated serum cholesterol value and there is no other evidence of endocrine gland failure. The test is most useful diagnostically when the symptoms and signs of hypothyroidism are equivocal, the basal metabolic rate is low, and the serum cholesterol value is normal or elevated. An accurate protein-bound iodine determination has already been shown to be a useful aid in the clinical differentiation of primary hypothyroidism from euthyroidism with only a small percentage of results being in error when performed in the best of laboratories.[19,20] An important disadvantage of this determination which limits its value or excludes its use in many laboratories is obtaining an accurate result due to the difficulty of the test [21,22] and the increasing shortage and rapid turnover of skilled laboratory technicians. In contrast the TSH test is much easier to perform and more definitive, and an unskilled technician can be quickly and easily trained to perform this test. The increasing availability of radioiodine for diagnostic use to smaller medical centers due to relaxation of restrictions by the Atomic Energy Commission has greatly enhanced the practicality of this test.

Although the I^{131} uptake itself without the use of TSH is a useful aid in ruling out hypothyroidism, the results overlap on primary hypothyroidism and euthyroidism in a significant percentage of patients, as reported by others [20,23] and observed in our own patients.

Our results indicate that a normal TSH test with a single small dose rules out primary thyroid failure, including two patients with postoperative hypothyroidism, but Schneeberg and associates [23] reported normal tests with repeated large doses of TSH in four of five patients with postoperative

hypothyroidism. They suggested that the normal tests resulted from stimulation of remnants of responsive thyroid tissue which are still able to concentrate I^{131} but do not form a sufficient amount of thyroxine. In an occasional apparently normal patient, the administration of TSH may not significantly increase the uptake.[7]

A normal TSH test in the euthyroid patient without goiter taking desiccated thyroid rules out primary hypothyroidism, and the drug can be discontinued. This observation is especially useful because in such a patient the administration of a moderate to large dose of desiccated thyroid usually has suppressed the I^{131} uptake to a low value, and other tests of thyroid function, including the protein-bound iodine determination, if available, are nondiagnostic. On the other hand, an abnormal TSH test in such a patient does not by itself establish the diagnosis of clinical primary hypothyroidism,[3,7] but could result from pronounced physiologic atrophy of the cells, especially if moderate to large doses of desiccated thyroid have been taken over a long period of time. When there is no substantiated history of hypothyroidism in such a patient with an abnormal TSH test, the desiccated thyroid should be withdrawn for two months and the patient's clinical status then reevaluated.

The TSH test seems to have only a limited practical value in differentiating primary thyroid failure from thyroid failure secondary to anterior pituitary failure. Our experience and that of others [24,25,27,28] indicates that only a small percentage of patients with nonsurgical anterior pituitary failure have characteristic clinical features of hypothyroidism, while others [29-31] have reported a higher percentage. Clinically, careful assessment of the history and physical examination, in our experience and that of others, [25-27] is sufficient to differentiate secondary hypothyroidism from primary hypothyroidism in most instances. Other laboratory studies of endocrine function may or may not be useful in differentiating primary and secondary thyroid failure.[26,31-35] Only two patients with clinical hypothyroidism secondary to anterior pituitary failure have been reported who had failure of thyrotropin production alone.[36,37] Both of these patients had normal TSH tests and were treated only with desiccated thyroid or *l*-thyroxine.

Unless the patient has clinical evidence of other endocrine failure associated with hypothyroidism, we do not believe it is necessary or practical to do a TSH test to rule out anterior pituitary failure as the cause in every patient with hypothyroidism. When thyrotropin is used to differentiate secondary from primary hypothyroidism, we agree with others that large repeated doses of TSH should be used instead of one small dose. The occurrence, reported by others [4,8,26,34] and observed in one instance by us, of abnormal TSH tests in a few patients with anterior pituitary failure even when repeated doses of TSH are given suggests that the thyroid cells have undergone some irreversible failure. Pathologically, this belief has been substantiated by Sheehan's [29] previous observations of extensive fibrosis, lymphocytic infiltration, and atrophy or disappearance of thyroid cells in the thyroid glands of some patients with anterior pituitary failure and has been confirmed by Perkins and Rynearson.[30]

Abnormal TSH tests in patients with Graves' disease who have been treated with radioiodine or surgery have in our opinion three possible causes: the hypertrophic thyroid cells have been damaged by I^{131},[16-18] some hypertrophic thyroid cells are still undamaged, or the normally functioning thyroid cells are decreased in number and are under maximal TSH stimulation.[17] When the damage to the thyroid cells from I^{131} is severe, clinical hypothyroidism results and the I^{131} uptakes usually are low. When the damage is milder, the I^{131} uptakes may be normal and the thyroid cells may or may not be under maximal TSH stimulation. Residual undamaged hypertrophic thyroid cells may concentrate I^{131} at the same high maximal rate as they did when hyperthyroidism was present but are not sufficient in number

to form excess thyroxine. These cells probably function independently of endogenous TSH from the pituitary gland in the same way after treatment as Werner and associates [16] have suggested they do before treatment. It is important to know that an abnormal TSH test with normal or high I^{131} uptakes may occur in euthyroid patients with Graves' disease who have been treated with radioiodine or surgery and that it does not indicate the presence of clinical primary thyroid failure unless there are other confirmatory clinical and laboratory findings.

In euthyroid patients with Graves' disease and unilateral or bilateral exophthalmos who have received no treatment, an abnormal TSH test favors the diagnosis and militates against other causes of proptosis, such as retro-orbital tumor and leukemia. However, as observed in four of our patients, a normal TSH test does not rule out Graves' disease as the cause of the exophthalmos.

Another most important use of the TSH test is in the preoperative differentiation of struma lymphomatosa from other types of nontoxic goiter, such as adenomatous goiter and carcinoma of the thyroid. Skillern and associates [10] recently reported that struma lymphomatosa is not a true thyroiditis but is idiopathic partial primary failure of the thyroid cells with compensatory hyperplasia of thyroid follicles and usually oxyphilia of the cytoplasm. The lymphocytic infiltration and fibrosis are probably secondary phenomena and together with oxyphilia of the cytoplasm of thyroid cells also occur in the thyroid glands of patients with primary hypothyroidism without goiter. Thus, struma lymphomatosa probably is the same disease as primary hypothyroidism without goiter, except that the initial degree of thyroid cell failure is much less, and the thyroid follicles are able to undergo compensatory hyperplasia in response to increased endogenous thyrotropin production from the pituitary gland. Increased thyrotropin production is due to the thyroxine deficiency. Because this increase in endogenous TSH production by the pituitary gland is already stimulating near maximally the iodide-concentrating function of the failing thyroid cells, 4 units of exogenous TSH does not cause a significant increase in I^{131} uptake.

In contrast, patients with nontoxic adenomatous goiter or carcinoma of the thyroid do not have an increase in endogenous TSH production and almost always show a significant increase in I^{131} uptake after TSH administration, due to stimulation of normally functioning thyroid cells still present. We should like to caution that many more TSH tests will have to be done in patients with carcinoma of the thyroid before this test can be conclusively regarded as a useful aid in the clinical differentiation of this condition from struma lymphomatosa or subacute thyroiditis.

Also, a patient with struma lymphomatosa and anxiety tension state may be difficult to differentiate clinically from a patient with Graves' disease and mild hyperthyroidism without the aid of thyroid function tests. The TSH test is likely to be abnormal in both of these diseases and is of little value in this differentiation.

The total protein-bound iodine (TPBI) values were normal in 13 of 14 patients in our series and were of little value as an aid to the diagnosis of thyroid failure in patients with struma lymphomatosa. This is true because the TPBI measures not only thyroxine but also a metabolically less active iodinated protein which Owen and McConahey [38] have reported is probably thyroglobulin and which is not proteolyzed into thyroxine by the failing thyroid cells. Butanol-extractable protein-bound iodine (BEPBI), which measures only thyroxine, was low in seven and low normal in seven other patients with struma lymphomatosa.

An accurate preoperative diagnosis of struma lymphomatosa is important because the treatment of struma lymphomatosa is medical and that of the other two types of goiter is surgical. Struma lymphomatosa is best treated by the administration of 3 grains of uncoated U. S. P. desiccated thyroid which corrects the varying degrees of asymp-

tomatic and symptomatic thyroxine deficiency and suppresses the TSH production of the pituitary gland, usually resulting in a significant decrease in the size of the goiter.

The TSH test usually is abnormal in patients with subacute thyroiditis because of damage to the thyroid cells secondary to probable true inflammation. Usually the clinical features of this disease are sufficient to differentiate it from struma lymphomatosa or other types of goiter. In atypical cases of subacute thyroiditis, an aid to differential diagnosis is the frequent occurrence of a low or low-normal I^{131} uptake that is usually not increased after the administration of TSH and a usually normal or elevated basal metabolic rate. However, a low basal metabolic rate may be observed in some patients in the late stage of subacute thyroiditis. Although the I^{131} uptake is usually normal or high in struma lymphomatosa, when it is low in struma lymphomatosa, the basal metabolic rate is low.

Summary

Measurement of the thyroidal uptake of radioactive iodine before and after the intramuscular administration of a small inexpensive dose of 4 units of thyrotropin (the TSH test) is a simple and, when correlated with other clinical and laboratory findings, a useful aid in the differentiation of certain nontoxic thyroid diseases with and without goiter. The thyroid-stimulating hormone test was normal when TSH produced a significant increase in the second I^{131} uptake as compared to the pre-TSH I^{131} uptake. Previous recent administration of inorganic or organic iodine will result in an abnormal TSH test with low I^{131} uptakes.

All of 32 untreated patients with normal thyroid function and 25 of 29 taking desiccated thyroid had a significant increase in I^{131} uptake after the administration of TSH. In contrast, 17 untreated and 11 treated patients with primary hypothyroidism had no such increase in I^{131} uptake after TSH.

Although a single small dose of TSH produced a significant increase in I^{131} uptake in 7 of 11 patients with anterior pituitary failure without clinical hypothyroidism, several injections of larger doses of TSH are necessary to differentiate secondary hypothyroidism from primary hypothyroidism. Even then the test is of only limited practical value for differentiating these two conditions.

The TSH test was abnormal in 30 of 31 patients with struma lymphomatosa, in contrast to the normal TSH test noted in 31 patients with nontoxic adenomatous goiter and 6 patients with carcinoma of the thyroid.

No significant increase in I^{131} uptake after TSH occurred in 12 of 14 patients with subacute thyroiditis and 5 euthyroid patients with surgically treated Graves' disease. The TSH test was normal in six of seven euthyroid patients with radioiodine-treated Graves' disease and four of six euthyroid patients with untreated Graves' disease with exophthalmos.

The TSH test was most useful in differentiating the euthyroid patient with questionable hypothyroidism from the patient with true mild to moderate primary hypothyroidism without goiter, the patient with normal thyroid function taking desiccated thyroid from the patient with true primary hypothyroidism taking desiccated thyroid, and the patient with struma lymphomatosa from one with nontoxic adenomatous goiter.

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The Cleveland Clinic Foundation, 2020 E. 93d St. (6).

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Serum Glutamic Oxalacetic Transaminase Activity in Experimental and Disease States

A Review

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Introduction

The measurement of serum enzymes has been a useful laboratory adjunct in the clinical resolution of diagnostic problems. The recent reports that have rapidly accumulated on the clinical application of alterations in serum glutamic oxalacetic transaminase (SGO-T) justify a review of the literature pertaining to this serum enzyme and to its clinical significance.

Transamination is a chemical reaction in which there is an exchange of the α-amino group of one amino acid for the keto group of an α-keto acid, with the resulting synthesis of a second α-amino acid and a new α-keto acid. This type of chemical conversion was first described in 1937 and was postulated to be a reaction which occurred with any amino acid and α-ketoglutarate or oxalacetate, using pigeon breast muscle as a source of transaminase.[9] In 1938, pig heart muscle was also shown to act as a transaminase.[29] In 1940, it was again shown that pigeon breast muscle and pig heart contained an enzyme which was capable of maximally catalyzing the transamination of 1 (+) glutamic acid and oxalacetic acid to form α-ketoglutaric acid and 1 (−) aspartic acid. Although this muscle enzyme was shown to transaminate other substrate systems, namely, glutamic-pyruvic, cysteic-oxalacetic, cysteic-α-ketoglutamic, aspartic-pyruvic, it was felt this reaction was more limited in scope than was originally postulated.[15,16] Subsequently, it was demonstrated using a coenzyme, pyridoxal phosphate, that muscle homogenates contained transaminase capable of catalizing the transfer of α-amino groups from 25 different amino acids and that this enzyme was present in pig heart, liver, and kidney tissue homogenates.[12] By 1952 it was reported that transaminase activity was not limited to pigeon breast and pig heart, liver, and kidney, but was present as well in varying activities in eight organs of the rat. Glutamic-oxalacetic transaminase (GO-T) was maximally present in heart homogenates, and to a smaller extent the enzyme was demonstrated in skeletal muscle, lung, brain, liver, spleen, prostate, and testes in decreasing order.[5] Subsequent observations indicated that the organ distribution of GO-T is species specific, and in man was present in heart, liver, skeletal muscle, and kidney in decreasing order.[49,55,69]

The maximal activity of glutamic-oxalacetic transaminase in cardiac musculature suggested that any alteration in heart-tissue metabolism might reflect itself in changes in the enzymatic activity of the blood. Accordingly, in 1953, the presence of GO-T was sought for and demonstrated in whole blood, serum, and plasma, and the range of normal serum activity for adults was delineated.[28] Concomitantly, elevations of SGO-T in the clinical course of some patients with acute myocardial infarction were observed.[30]

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Methods of Measurement of SGO-T Activity

Serum glutamic-oxalacetic transaminase has been measured chromatographically,[27,28] spectrophotometrically [20,27,45,52] and colorimetrically.[11] *

Quantitative paper chromatographic analysis permits the measurement of SGO-T by estimating the amount of glutamic acid formed during an 18-hour incubation period. Using this method the mean SGO-T activity expressed as micromoles per milliliter per hour of glutamate formed is 0.622 ± 0.191.[27,28] The chromatographic technique, although accurate, is cumbersome and lengthy.

Spectrophotometrically, SGO-T is assayed by employing a double enzyme system. Glutamic oxalacetic transamination is coupled to the enzymatic oxidation of reduced diphosphopyridine nucleotide, using either malic dehydrogenase or lactic dehydrogenase.[20,27,45,52] All of the spectrophotometric techniques measure SGO-T by estimating the rate of the enzymatic reaction rather than any one of the end-products of the transamination. Spectrophotometrically, SGO-T activity is expressed as units per milliliter of serum per minute. One unit equals a decrease in optical density of 0.001 mμ under the conditions specified in the literature. The mean activity of normal adult sera is 22.1 ± 6.8 units with the range of normal 5 to 40 units.[27] Although simple, rapid, and accurate, these techniques require malic dehydrogenase or lactic dehydrogenase, and these reagents are expensive, unstable, and not generally available.

The colorimetric method estimates SGO-T activity by measuring the amount of pyruvic acid formed under standard incubation conditions.[11] The oxalacetic acid formed by transamination is converted by aniline citrate to pyruvic acid. This method is simple and requires no enzymes as reagents, but it is somewhat less accurate than the other methods. Colorimetrically, SGO-T is expressed as units per milliliter of serum. One unit equals the formation of 1γ of pyruvate under the conditions specified. The mean activity of normal adult sera is 16.4 ± 8.4 units, with a range of normal 4 to 40 units. Transaminase activity has been found in all human and animal sera tested both in the normal and diseased state.[27]

The stability of this serum enzyme is such as to facilitate its clinical usefulness. Specifically, freezing and lyophilization of serum fail to influence SGO-T. Sera and plasma have equivalent activities, and storing at room temperature for 24 hours or at 4 C for 5 days does not significantly alter SGO-T activity. The fasting state does not influence SGO-T levels, and the variations from day to day in SGO-T in the same normal adult are insignificant.[14,27] The mechanism for excretory and/or secretory handling of SGO-T is unknown, but the presence of this enzyme in small amounts in urine and in large amounts in bile suggests that renal and biliary routes may contribute in this regard.[18] It is pertinent however, that oliguria and/or azotemia are not necessarily associated with elevated SGO-T activity.[31]

* Other techniques have been utilized for the measurement of glutamic oxalacetic transaminase activity in tissues other than blood; manometrically [12,35]; spectrophotometrically,[35] and chromatographically.[12,18,34,47]

Alterations of SGO-T Activity

Experimental and Clinical Cardiac Disease States

Alterations in SGO-T activity associated with myocardial infarctions have been studied experimentally by three techniques.[1,2,4,22,49,59] Simulating the pathological process of human transmural myocardial infarction, coronary occlusion by coronary artery ligation in the closed-chest dog has been produced and alterations in SGO-T correlated with electrocardiographic and other observations.[49,59] When the dogs died from experimentally produced infarction and/or were killed at varying periods following coronary ligation, normal and infarcted cardiac tissues were assayed for GO-T.[49] A rough correlation existed between the peak SGO-T elevation, the duration of SGO-T rise, and the size of the infarct produced. An infarct of less than 1 gm. of muscle mass in the dog was observed to produce elevations of SGO-T above the normal range of activity. It was postulated that the mechanism for increased SGO-T following experimental myocardial infarction was the leakage from infarcted muscle of GO-T which found its way into the serum. This hypothesis rested on the observations that infarcted muscle contained less GO-T than adjacent normal cardiac tissue of the same animal and that the older the infarct the less GO-T activity demonstrable in the necrotic musculature.[39,49]

Using an experimental technique by which plastic spheres were embolized into the coronary arteries of the closed-chest dog, myocardial infarction of predetermined extent was produced.[1,2,4] It was observed that

a relatively linear relationship existed between the size of the estimated infarct at autopsy and the peak rise in SGO-T activity. This peak rise usually occurred on the 9th to the 24th hour post infarction. As little as 10% infarction of the cardiac muscle mass produced significant elevations of SGO-T. When myocardial necrosis was produced by intravenous injection of papain into rabbits, elevations of SGO-T activity have also been observed.[49]

By the use of temporary occlusion of coronary arteries in dogs, myocardial ischemia of varying duration has been produced,[55,59] and the degree of ischemia correlated with electrocardiographic changes, SGO-T alterations, and heart tissue GO-T activity.[55] With a few exceptions, myocardial ischemia in the presence of confirmatory electrocardiographic changes without histologic necrosis resulted in no significant elevation in SGO-T activity. However, when ischemia resulting from experimentally produced coronary insufficiency was prolonged enough to result in morphologic evidence of tissue necrosis, SGO-T was increased above the normal range.[55]

Viral myocarditis experimentally produced in rabbits was associated with cardiac tissue necrosis and resulted in elevation in SGO-T activity in proportion to the extent of necrosis. When experimental viral pericarditis was produced, no elevations in SGO-T were observed.[58] This is in agreement with the observation that experimentally produced pericarditis in dogs was in most cases accompanied by no significant rise in SGO-T.[55]

Experimentally produced pulmonary infarction has been observed to be associated with no significant alterations in SGO-T.[3,55]

Transmural myocardial infarction in the human adult is associated with a rise in SGO-T activity which first becomes manifest 6 to 12 hours after the estimated time of coronary occlusion.[13,30-32,56,60] The rise in serum enzyme activity reaches a peak in 24 to 48 hours, returning to the normal range by the fourth to seventh day post-infarction.[13,31,56] The peak elevations noted following myocardial infarction are 2 to 15 times normal levels.[2,13,31] The peak rise and duration of abnormal serum activity is proportional to the size of the infarction and/or the degree of myocardial necrosis. This is in keeping with the experimental evidence in dogs,[1,31,44,59] and the clinical observation that a poor prognosis is implied when SGO-T activity exceeds 200 units at its peak rise[13] post infarction. However, a small myocardial infarction with slight tissue necrosis and a rise in SGO-T of less than 200 units does not necessarily imply a favorable prognosis. Following myocardial infarction the rise in SGO-T is not influenced by or correlated with shock, blood pressure, heart failure, location of the infarction, anticoagulants, digitalis, quinidine, age, sex, color, temperature, weight, sedimentation rate, white blood cell count, or oliguria.[31] The rise in SGO-T following infarction is not necessarily correlated with the configuration of the electrocardiogram.[31] It has been suggested that the peak rise in SGO-T activity is roughly proportional to the size of the infarction as reflected electrocardiographically, although admittedly the latter presents poor criteria for evaluating the extent of myocardial necrosis.[31] When the electrocardiogram is not diagnostic or is obscured by previous myocardial infarction, bundle-branch block, Wolff-Parkinson-White syndrome, and other electrocardiographic changes, the rise in SGO-T activity in a clinical setting suggestive of infarction is an especially useful clinical tool.[31] Secondary rises in SGO-T activity have been observed in patients who following acute myocardial infarction present clinical stigmata consistent with extension of the infarction.[31] It has been suggested that changes in SGO-T activity may contribute in delineating the process of myocardial necrosis in patients with substernal pain, not only with suspected coronary occlusion but also in the presence of coronary insufficiency without occlusion.[2,13,31,32,55,60] It appears that SGO-T activity remains within

normal limits in patients with status anginosis or severe coronary insufficiency in spite of accompanying transient ST segment and T wave abnormalities.[13,31,55] When in this clinical setting SGO-T activity is elevated, it is presumed that ischemia has been accompanied by and/or followed by myocardial necrosis.[31,55]

Failure to find the characteristically described elevations in SGO-T following myocardial infarction usually can be attributed to failure to get early and serial SGO-T determinations.[69]

Otherwise uncomplicated instances of cardiac arrhythmias, unless associated with a ventricular rate of 180/minute or more, have not been reported to be associated with significant rises in SGO-T.[13] Although it has been stated that acute rheumatic carditis in children and young adults may be associated with rises in SGO-T activity,[52-54] recent extensions of these studies indicate that with some exceptions the rise of SGO-T activity in patients with rheumatic fever appears to be correlated with salicylate toxic hepatitis rather than degree of cardiac tissue injury.[38]

Pericarditis of various causes [55,58,67] and pulmonary emboli [3,13,30,55] with and without pulmonary infarction have been observed to be associated with no significant elevation in SGO-T activity. SGO-T has been suggested as an additional diagnostic tool in the differentiation of pulmonary and myocardial infarction.[23]

Experimental and Clinical Hepatic Disease States

Experimentally produced virus hepatitis in mice has been associated with increase in SGO-T activity. A relationship appears to exist between the rise in SGO-T activity and the size of the virus inoculum, the blood virus titer, and the degree of liver necrosis.[19] The injury to hepatic tissue accompanying partial hepatectomy in mice is associated with elevations in SGO-T.[19] When hepatocellular injury was produced in rats with carbon tetrachloride, it has been observed that SGO-T alteration serves as a sensitive index of hepatocellular injury.[40-42] The height and duration of increased SGO-T activity has been found to be proportional to the amount of toxin administered and to the extent of liver cell damage.[40] It has been reported in experimental carbon tetrachloride toxic hepatitis that hepatic tissue GO-T is not decreased even when SGO-T is markedly elevated.[43] Cirrhosis and hepatic tumors experimentally produced in rats with butter yellow [18] have been shown to be accompanied by elevated SGO-T activity.[42]

Common-duct occlusion experimentally produced in dogs has resulted in elevations in SGO-T activity which returns to normal within a week following the relief of biliary-tract obstruction.[20]

Acute hepatic disease has been noted to be associated with rises in SGO-T activity. In most instances, the quantitative and serial changes in SGO-T observed are sufficiently characteristic of the various types of liver disease to assist in diagnostic differentiation.[13,63] The largest elevations in SGO-T activity have been observed in acute toxic hepatitis due to carbon tetrachloride [63] and in patients with acute infectious and/or homologous serum hepatitis.[13,63] The rise in SGO-T following exposure to carbon tetrachloride occurs within 24 hours and has been reported to reach levels as high as 27,000 units.[63] With cessation of exposure to the toxin, SGO-T precipitously falls toward normal. Toxic hepatitis due to chlorpromazine (Thorazine),[13,68] salicylate,[38] cinchophen,[37] Azaserine (O-diazoacetyl-L-serine)[69] pyrazinamide,[68] and other agents is associated with smaller elevations of SGO-T than have been observed in carbon tetrachloride toxic hepatitis.[13,68] However SGO-T increases proportionally with the continued administration of these drugs when they prove to be hepatotoxic. Discontinuance of the hepatotoxic drug results in a rapid fall of SGO-T toward normal.[69]

Acute infectious and homologous serum hepatitis result in alteration of SGO-T [13,63,65,68] to levels 10 to 40 times greater than normal.[63,67] It would appear that the rise

in SGO-T in virus hepatitis begins during the prodromal phase of the disease,[67,68,70] reaching a peak elevation at the time the patients are the sickest as adjudged by fever, malaise, anorexia, nausea, vomiting, and hepatic tenderness.[13,63] With subjective and objective clinical evidence of improvement, hepatitis is accompanied by a fall in SGO-T toward normal.[13,63] Relapse and/or the development of chronic hepatitis is reflected in continued abnormal SGO-T levels.[63,68,70] It has been suggested that the serial and quantitative changes in SGO-T during the course of hepatitis reflect the clinical state of the patient better than conventional liver function tests.[63] In this regard SGO-T is said not to reflect liver function per se, but rather acute liver cell injury,[63] and accordingly is found not to correlate necessarily with the routinely employed tests of liver function.[13,63]

Infectious mononucleosis is usually accompanied by normal SGO-T activity.[69] However, when this condition is associated with hepatitis there is a rise in SGO-T [13, 63,68] at a time when liver function may be normal or inconclusively affected as measured by conventional tests. The severity of the hepatitis accompanying infectious mononucleosis appears to be related quantitatively to the peak rise in SGO-T.[63,70]

Active or decompensated Laennec's cirrhosis is associated with elevations in SGO-T activity in the range of 50 to 250 units.[13,63] Biliary cirrhosis is generally accompanied by somewhat greater elevations than Laennec's cirrhosis.[45,69] Cirrhosis complicated by acute hepatitis has been reported to present SGO-T alterations characteristic of acute hepatitis, but superimposed on the serum enzyme elevation due to hepatic cirrhosis.[63] It has been suggested therefore that SGO-T may be used to determine whether one is dealing with sudden hepatic decompensation secondary to cirrhosis or superimposed acute hepatitis in the cirrhotic patient.[63]

Extrahepatic and intrahepatic biliary-tract obstruction are accompanied by elevations in SGO-T to levels as high as 300 units.[13,45, 63,67] Relief of biliary obstruction, as in the surgical removal of common-duct stones or pancreatic tumor, results in a fall in SGO-T toward normal within 7 to 14 days.[63] SGO-T activity in cirrhosis and biliary-tract obstruction as in other forms of liver disease has not been found to parallel or correlate with tests of liver function.[63] It has been reported that in obstructive jaundice SGO-T may follow the course of the serum bilirubin.[13] The rises in SGO-T which have been reported to accompany acute pancreatitis may be explained as being due to transient common-duct obstruction.[69] Whether pancreatic necrosis without biliary-tract obstruction may lead to SGO-T elevation is not clear.

Primary and metastatic carcinoma of the liver are both associated with elevations in SGO-T. Increased SGO-T activity appears to be a sensitive index of neoplastic involvement of the liver,[13,67] except with the lymphomas and leukemias,[67] where SGO-T is usually within the normal range.

Elevations in SGO-T in primary and secondary carcinoma of the liver, extrahepatic obstructiive jaundice, and cirrhosis of the liver may be so similar as to be of little value in differential diagnosis.[67]

It is pertinent that normal SGO-T activity has been reported in most instances of nonmalignant and malignant bone disease in the absence of hepatic involvement, whereas many of these cases were associated with elevations in serum alkaline phosphatase.[67] Therefore, elevations in alkaline phosphatase due to bone disease may be differentiated from those due to liver disease because SGO-T is not elevated in bone disease. Clinically, this test may be of special value when one is in doubt as to whether an elevated serum alkaline phosphatase is secondary to bone or to liver disease.[67]

Experimental and Clinical States Other Than Cardiac and Hepatic

In the absence of injury to the heart, liver, skeletal muscle, and kidney tissue, no

significant alterations in SGO-T activity have been observed in neoplastic, allergic, infectious, congenital, degenerative, metabolic, and reactive or collagen disease states.[13,67] Surgery in dogs[49] and in humans[63] resulting in injury to skeletal muscle is associated with a transient rise in SGO-T activity, with return to normal in one to four days.[63] Elevations reported are of the order of 50 to 200 units in the experimental situation[49] and up to 100 units in the clinical setting.[69] Abnormal SGO-T activity has been observed in patients with dermatomyositis.[31] Gangrene of skeletal muscle associated with atherosclerosis and/or arterial emboli has been associated with normal or elevated SGO-T activity.[69] Thrombophlebitis has not been reported to cause elevations in SGO-T.[13, 31,67]

Although acute and chronic renal disease, azotemia, and uremia have not been found to be associated with elevations in SGO-T,[13,31,67] no extensive experience with renal infarcts has been reported. In the experimental production of graded renal infarcts in dogs by arterial ligation,[57,59] it has been observed that SGO-T rises above the normal range in proportion to the size of the infarct. The infarcted renal tissue was noted to contain one-third to one-fourth the enzyme activity of the uninfarcted kidney tissue.[57]

The appreciable activity of GO-T in brain[5] does not appear to result in alterations of SGO-T in various types of infections and degenerative, vascular, and other disease states of the nervous system.[13,67] It has been suggested that there is a blood-brain barrier to GO-T.[31] This hypothesis stems from these clinical observations as well as from the experimental fact that in dogs after death, the blood reservoirs draining tissues rich in GO-T show progressive and impressive rises in SGO-T activity, with the exception of the jugular venous blood.[21,31]

Serum and plasma usually contain similar SGO-T activity.[27] However, platelet-poor plasma has been reported to have decreased SGO-T activity. Platelets have been shown to contain GO-T activity.[36] No reports on patients with thrombocytopenia have appeared. In addition to serum, plasma, and platelets, blood hemolysates have been shown to contain about 10 times the activity of GO-T found in serum.[27,31]

An extensive study of SGO-T during various stages and conditions of pregnancy has shown no significant alteration of the serum enzyme above the normal range.[7] Elevated SGO-T has been reported in eclampsia[7] and preeclampsia.[13] It appeared from this study[7] that the mean activity of SGO-T during pregnancy was somewhat lower than the mean activity of SGO-T in normal nonpregnant adults. The experimental production of intrauterine death in pregnant mice failed to cause a rise in SGO-T activity.[47]

Summary

A review of the literature and unpublished data dealing with alterations in SGO-T activity in various experimental and disease states is presented.

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Is the Postcommissurotomy Syndrome of Rheumatic Origin?

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Soon after mitral commissurotomy became a frequent procedure, a clinical syndrome characterized by the occurrence of recurrent febrile episodes associated with pleuritis, pericarditis, pneumonitis, and occasional joint pains was recognized. Janton [1] (1952) was the first to call attention to this syndrome, which he called "pleuropericardial episodes." He considered it to be due to smoldering rheumatic activity, but found that direct evidence for this was lacking. In 1955 he wrote [2] that in 8 of 41 living patients, there had been repeated postoperative episodes certain to be regarded even without laboratory verification as rheumatic activation. Soloff [3] stated "Because of the frequency of this syndrome following mitral commissurotomy and its absence following any other non-rheumatic cardiac or pulmonary surgery, and because of the frequent cardiac involvement, the syndrome should be regarded as reactivation of rheumatic fever." At first, most opinion was in agreement with that of Janton and of Soloff, but further observations have necessitated a reorientation.

This paper consists of an examination of the available evidence as to its etiology and of our personal experience with the postcommissurotomy syndrome. The various factors for and against the rheumatic etiology of the postcommissurotomy syndrome, utilizing data obtained from clinical, physiological, serological, and pathological studies, will be considered.

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We shall first discuss the evidence that has been considered to indicate that rheumatic fever is responsible for this syndrome.

Evidence That Rheumatic Fever is Responsible

1. Occurrence of the Syndrome

The observation that this syndrome occurred after surgery on the heart or chest, only in patients with rheumatic heart disease, was important in leading to the concept that a reactivation of rheumatic fever was responsible. For a time, this seemed to be true, but after more extended observation, cases were observed after operations for pulmonary stenosis [6,7] and also in congenital and arteriosclerotic heart disease when the pericardium had been incised at operation.[8,9] Bailey [8] and Harken [9] have seen similar episodic and recurrent bouts of fever, at times associated with myalgia or arthralgia, occurring frequently following cardiac surgery on adult patients with obviously nonrheumatic lesions.

Sir Russell Brock [10] has seen a "considerable incidence of this so-called postcommissurotomy syndrome when operating on the heart in congenital heart disease in the absence of rheumatic fever." Perianes [11] had noted a higher percentage of the postcommissurotomy syndrome in patients in whom the heart was approached through the anterior rather than the posterolateral wall. Andrus and Blalock [12] have seen the syndrome on occasion following surgery for congenital defects, and Papp and Zion [31] have seen a case following a Blalock anastomosis.

2. Cyclic Nature of the Syndrome

The cyclic nature of the syndrome, with recurrent attacks reminiscent of the rheu-

matic process, has been used as a good point in favor of the rheumatic etiology. Acute benign recurrent nonspecific pericarditis also shows such a phenomenon and is not ordinarily considered of rheumatic origin. Dressler [14] has used this feature to link the latter condition with the postcommissurotomy syndrome in a provocative but inconclusive discussion. He has also described a postmyocardial infarction syndrome which is also cyclic and recurrent and yet is distinctly not of rheumatic origin. We shall consider this syndrome again later.[15]

3. Hypersusceptibility to Nonspecific Stimuli

Some have considered the syndrome to be an example of the hypersusceptibility of the rheumatic patient to nonspecific stimuli. There have been reports on the relation of trauma to rheumatic activity.[4,5] Subcutaneous nodules, clinically indistinguishable and histopathologically similar to those occurring spontaneously, have been produced in patients with rheumatic fever by injecting autologous blood into the subcutaneous and deep tissues of the olecranon process, followed by frictional pressure. The more active the rheumatic fever, the larger the induced nodule and the longer its duration. Nodules were produced in 90% and 50%, respectively, of patients with clinical and subclinical rheumatic fever and in only 3% of normal controls.

This question of trauma has been discussed from another point of view by Stollerman,[16] with logical rebuttal of the significance of the observations of Massell, Mote, and Jones. He stated that the delayed appearance of a syndrome of chest pain and fever suggested reactivation of rheumatic fever. However, from preliminary data the postcommissurotomy syndrome did not appear to be related to recent streptococcal infection. It also appeared unrelated to many other factors which would be expected to correlate with persistence of the chronic rheumatic state, such as the presence of Aschoff bodies in the myocardium, the interval since the last rheumatic episode, or the patient's age.

If it were assumed that the postcommissurotomy syndrome were a reactivation of rheumatic fever, it would indicate that direct surgical trauma to the heart can exacerbate the rheumatic process. This would imply that the rheumatic state persisted as a potential specific tissue reaction to injury other than streptococcal infection. No evidence has been proposed to indicate that trauma could be important in producing recurrences of rheumatic fever. In young subjects with rheumatic fever who had received antistreptococcal prophylaxis at Irvington House, rheumatic recurrences had not been observed after fractures, immunization procedures, intravenous administration of typhoid vaccine, a wide variety of acute diseases, or anything but a new Group A streptococcal infection.

Miller, Kibrick, and Massell [17] explored the possibility in subjects with rheumatic fever of a peculiarity of immune response which would predispose to the rheumatic state.[18,19] Their studies were aimed to determine whether such supposed immunologic hyper-reactivity of rheumatic subjects were confined to the Streptococcus alone or if a more general augmentation of antibody response to nonstreptococcal antigens existed as well. Using both viral and bacterial antigens, they were unable to attribute to these rheumatic patients any general hyperreactivity of immune response as an explanation for the development of the rheumatic state.

4. Response to Salicylates

The beneficial response to salicylates in large doses can no longer be considered to be diagnostic of rheumatic fever. Too many instances of the salutary response of other nonspecific inflammatory conditions have been observed to maintain this as pathognomonic evidence. On the other hand, Dresdale [25] had noted a gradual defervescence or no effect at all in treating the postcommissurotomy syndrome with salicylates. Bercu [23] has had similar experiences. Elster, Wood, and Seely [20] have noted a more favorable response. One can conclude that

a uniformly favorable response does not occur and that even if it did, it would not constitute evidence for a rheumatic etiology.

5. Fibrinous Pericarditis

Recurrent episodes of fibrinous pericarditis without large effusions occur not only in acute rheumatic fever and in this syndrome, but also in idiopathic pericarditis and in the postmyocardial infarction syndrome. This point is, therefore, of no value in establishing a rheumatic etiology.

6. Prolongation of the P-R Interval

While prolongation of the P-R interval during an episode of the postcommissurotomy syndrome has occurred on occasion, this certainly should not be considered diagnostic of rheumatic fever unless accompanied by other more distinct evidences. A temporary prolongation of the P-R interval has been noted in a variety of entities other than rheumatic fever.[34]

7. Absence of the Syndrome in Coronary Artery Disease

The absence of the syndrome in 150 cases of cardiopericardiopexy in patients with coronary artery disease but its appearance in one patient with mitral stenosis in whom only the pericardium was entered[20] has been offered as evidence. The exact significance of this is difficult to evaluate.

8. Development of the Syndrome When No Commissurotomy Performed

The chance observation of the development of the postcommissurotomy syndrome in a patient with rheumatic heart disease in whom the auricular appendage had been incised but in whom a commissurotomy was not performed, led to the use of the term "the post-cardiotomy syndrome."[25] On the other hand, Elster and co-workers[20] noted that one case in which only pericardiotomy had been done (the heart muscle was not incised) developed the postcommissurotomy syndrome three weeks later. These observations do not readily lend support to either a rheumatic or nonrheumatic etiology for the postcommissurotomy syndrome but are certainly of great interest.

Evidence That Rheumatic Fever is Not Responsible

A good deal of evidence has been brought forth to indicate that the syndrome under discussion is not of rheumatic etiology.

1. Failure to Demonstrate Antecedent Streptococcal Infections

The failure to demonstrate antecedent streptococcal infections in all but rare exceptions, as indicated by the absence of a rise in the antistreptolysin-O titer, except in a very small percentage of cases of the postcommissurotomy syndrome,[13,20,25,31] is of extreme importance.

2. Failure of Penicillin Chemoprophylaxis

Penicillin chemoprophylaxis has failed to prevent the syndrome.[20,31] There has been no change in the frequency of occurrence, the character, the intensity, or the duration of the illness. This could probably exclude latent streptococcal infection.

3. No Relationship to Presence of Aschoff Bodies

The absence of a relationship between the occurrence of the syndrome and the presence of Aschoff bodies in the auricular appendage biopsies taken at the time of commissurotomy would appear to be of great significance.

Glover and Janton[2] noted that although the auricular appendages in 12 of 41 patients showed "rheumatic stigmata," there was no clinical evidence of rheumatic activity. On the other hand, in 8 patients with the postcommissurotomy syndrome, only 3 showed "rheumatic" changes in their appendages. Similar findings have been reported by others,[3,20,22,25] also pointing to the fact that no correlation has been shown to exist between Aschoff bodies and the occurrence of the syndrome. Perhaps, utilization of the criteria of Tedeschi, Wagner,

and Pani [24] of two categories of Aschoff bodies might be more rewarding. They noted an early acute lesion with exudative changes and a chronic, senescent, fibrotic, or healed phase. In 400 consecutive biopsies of the left auricular appendage, only 8 specimens, or 2%, showed active lesions, although a total of 75 specimens, or 18.8%, showed Aschoff bodies. A comparison of the incidence of the postcommissurotomy syndrome with so-called "active" early acute bodies would be of great interest.

4. Inconclusive Evidence of Rheumatic Sequelae

The inconclusive evidence of rheumatic carditis or of other rheumatic sequelae and the lack of a significant number of instances of restenosis in patients who develop the syndrome is rather striking. Should there be a high incidence of reactivation of rheumatic fever in the postoperative period one would expect a high incidence of restenosis. Several reports may be mentioned in this respect. Two instances [26,31] of restenosis were found to be associated with rheumatic activity and another [28] with no autopsy evidence of activity. Glover and co-workers [27] found no recurrent mitral stenosis in studies of 600 cases, including 31 followed to autopsy. Verheugt [30] found no evidence of rheumatic activity in several cases studied at postmortem examination. A well-conceived clinical study [31] showed that the valves and myocardium were unaffected and that the postcommissurotomy syndrome did not prolong the P-R and Q-T intervals.

Bailey and Bolton [21] have noted restenosis in 13 of 1000 cases at from 18 months to 66 months postoperatively with no evidence of active rheumatic fever. This incidence of restenosis in 1.3% contrasts sharply with the reported 25% to 50% incidence of the postcommissurotomy syndrome and makes it difficult to invoke rheumatic reactivation. From this evidence, one could conclude that restenosis occurs irrespective of rheumatic activity and that its low incidence suggests no relation at all to the postcommissurotomy syndrome.

5. The Syndrome in Patients with Pulmonary Stenosis and Interatrial Septal Defect

The syndrome has been recognized in the postoperative state in patients with pulmonary stenosis and interatrial septal defect [6] as well as in other types of congenital heart disease.[7,10,11,12]

6. Development of Rheumatic Fever Postoperatively

The general experience has been that a small number of patients develop unequivocal active rheumatic fever postoperatively. Most of these have not developed the classic postoperative commissurotomy syndrome. For example, Ellis and Harken [22] have reported that while 7% of 500 patients studied after mitral commissurotomy showed good clinical evidence of rheumatic fever or arthritis, 31% showed evidences of the postcommissurotomy syndrome. They believe that patients who develop symptoms of congestive failure following operation may do so because of a physiologic adjustment to the change in hemodynamics occasioned by effective fracture of the mitral valve, rather than from rheumatic activity. The left ventricle, previously protected by severe mitral stenosis, may take months to hypertrophy and accommodate itself to an increased work level. In this respect, they differ with Soloff and Zatuchni,[24] who felt that cardiac enlargement and failure postoperatively could be used as an indication of rheumatic activity. Dresdale and co-workers [25] also noted that although pathologic evidence for myocarditis is not conclusive, a deterioration of the cardiac reserve should make one suspect rheumatic activity.

7. Similar Syndrome Occurring After Myocardial Infarction

The recent description [10] of a similar syndrome occurring after myocardial infarction in patients without rheumatic fever has been discussed above.

If, then, the bulk of evidence opposes the view that this syndrome represents reactivation of rheumatic fever, what are the

possible alternatives? Soloff [3] has suggested several possibilities: 1. The operation permits spread of endogenous streptococci, with the delayed appearance of the syndrome after a latent period; 2. the operation increases susceptibility to mild and subclinical streptococcal infections; 3. surgical incision of inflammatory tissue spreads inflammatory agents; 4. surgical incision permits the escape of abnormal protein material to which immune bodies are produced, giving clinical manifestations; 5. this syndrome is an example of the hypersusceptibility of rheumatic patients to nonspecific stimuli.

Bailey and Bolton [21] considered that the febrile episodes were due to (1) absorption of degenerated blood constituents; (2) pulmonary atelectasis; (3) pulmonary infarction; (4) bacteremia or septicemia; (5) embolic visceral infarction; (6) occasional undeniable rheumatic exacerbation.

Papp and Zion [31] believe that local factors cause the postcommissurotomy syndrome. They feel that the syndrome is an accentuation, persistence, and recurrence of the normal postoperative sequelae, being caused by postoperative oozing from the auricular wound, as shown by the blood-stained effusion causing a recurrent pleuropericarditis; loculation of the effusion and left basal lung consolidation constitute additional factors. They remark that the early cases were not recognized. At first they were thought to be due to (1) too tight pericardial suture; (2) pericarditis caused by incorrect pH of procaine (novocain) solution injected into the pericardial sac; (3) chest pain and pyrexia from postoperative auricular thrombosis; (4) left basal pneumonia.

Several other clues to a possible etiologic mechanism should be considered. Dressler [15] has recently described 20 patients exhibiting a train of events that he designates the postmyocardial infarction syndrome. Cyclic, recurrent, febrile episodes with pericarditis, pleuritis, and pneumonitis comprise the clinical features which have a surprising similarity to the postcommissurotomy syndrome. It might represent an isoallergic response to the patient's own heart muscle and suggests a possible theory for the occurrence of the postcommissurotomy syndrome as well. The studies by Cavelti,[32,33] in which autoantibodies to heart, skeletal muscle, and connective tissue were produced experimentally, points up the possibility of an isoallergic mechanism [30] in the postcommissurotomy syndrome and in the post-myocardial-infarction syndrome.

Other experimental findings are of great interest in this connection. Many workers,[36-40] using a Freund adjuvant (serum and paraffin oil mixtures plus autologous tissue), have produced isoallergic encephalomyelitis and neuritis. Recently Pearson [41] has produced arthritis, periarthritis, and periostitis in rats from 14 to 45 days after the injection of macerated striated muscle tissue in a Freund type adjuvant. A recent report [42] of 10 autopsies showing "Atypical Pulmonary Inflammatory Reactions" in association with 3 cases of myocardial infarction and several miscellaneous cases is of interest. The authors suggested either a viral etiology or an allergic response, as proposed by Rich and Gregory.[43] The findings included Masson bodies (organized plugs of fibrinous exudate previously considered almost specific for rheumatic pneumonia), fibrinoid swelling of the walls of alveoli and blood vessels, monouclear-cell exudates, hyaline membranes, and fibrinous plugs. While at present the pathology of the pneumonitis in the postcommissurotomy syndrome and in the post-myocardial-infarction syndrome is unknown, it is possible that it will be in the same category as these "atypical pulmonary inflammatory reactions."

Thus, it is attractive to speculate that the postcommissurotomy and similar syndromes might be due to the development of isoallergic immune bodies to altered tissues in certain persons.

Summary and Conclusions

The present day concepts of the postcommissurotomy syndrome are reviewed.

The evidence concerning a reactivation of rheumatic fever as its etiology appears insufficient to be accepted.

It has been speculated that this syndrome may be a hypersensitivity state which is not peculiar to patients with rheumatic fever alone.

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Treatment in Internal Medicine

Treatment of Diabetic Acidosis

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Effective treatment of diabetic acidosis is based on three important prerequisites: 1. systematic efforts at prevention; 2. accuracy of diagnosis; 3. correct appraisal of severity.

Prevention succeeds when both patient and physician are aware of the causes of acidosis and avoid them. Some of the most common are omission or delay in daily insulin administration; reduction in insulin dosage because food cannot be taken during illness; increased insulin need during acute infection and trauma; failure to test urine for ketones when heavy glycosuria exists; disdain toward warning symptoms, especially thirst, polyuria and nausea; complacent attitudes toward poor routine control of diabetes.

Precise diagnosis often reveals a cause for acute illness in diabetes other than acidosis, even when glycosuria with some ketonemia, ketonuria, and lowered alkali reserve are present. A diabetic in coma is not necessarily in diabetic coma. Some of the sources of confusion are insulin shock; cerebral trauma, hemorrhage, or thrombosis; myocardial infarction with shock; hepatic coma; acute alcoholic or barbiturate intoxication. Such diseases occur in diabetics as often as in others—in some cases, such as insulin shock and vascular accidents, even more so. Heroic therapy, as for severe diabetic acidosis, may then obviously cause death, not prevent it. Probably some of the high mortality rates still reported for "diabetic coma" are due to failure to distinguish between severe diabetic acidosis as a sole cause of the existing illness and mild acidosis as a consequence of some other cause.

Shrewd appraisal of severity of proven diabetic acidosis usually determines the intensity and hence success of treatment. Since almost all diabetic acidosis (even in "insulin-resistant" patients) is dramatically reversible at the will of patient and physician, failure can usually be attributed to lack of ability to judge the depth of acidosis or to employ vigorous therapy promptly. Only acidosis which has progressed to a very late stage needs to be fatal, and even then skillful handling may reverse it. Useful guides in estimation of severity may be summarized as follows.

Clinical.—Increasing depth of acidosis is indicated early by nausea and vomiting, often with abdominal pain. Later, increasing stupor and shortness of breath are better guides. Very late, breathing becomes shallow and shock signs appear, notably, hypotension, tachycardia, and oliguria or anuria. Only then does coma appear.

Chemical.—Blood and urine sugar levels are not of great value, except that when the blood sugar exceeds 500 mg. per 100 cc. acidosis is likely to be present and severe. Very high sugar levels are due to failure of excretion of sugar, as a rule, indicating renal or circulatory failure. Plasma ketone levels, on the other hand, are extremely helpful. Values of 50 to 200 or more milligrams per 100 cc. are diagnostic. Simple bedside methods which can provide data within a few minutes (if materials are kept readily available) have been devised by Duncan [1, 2] and Guest.[3]

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The plasma carbon-dioxide combining capacity can give valuable information. In well-organized laboratories determinations can be obtained promptly. Severe acidosis is present only when values are below 9 mEq., or about 20 vol. %. Values below 4 or 5 mEq., or about 10 vol. % are of grave import.

With such an abundance of simple diagnostic criteria there is little excuse for inaccurate diagnosis or faulty appraisal of severity. By their use treatment can and should be effective in all but a few late cases. Root reports the mortality at the Joslin Clinic to be only 3.2% in about 400 cases during the last two decades.[4]

Treatment of Mild Acidosis

Asymptomatic cases with blood sugar and plasma ketone and alkali values less abnormal than those described above may be managed simply with modest measures. Such patients are usually spoken of as being "ketotic" or "in ketosis" rather than in acidosis. This is not a valid distinction, however. Chemically they can be shown to be in acidosis, like their sicker counterparts, but only slightly or moderately so. The distinction is a quantitative one, not qualitative.

Supplementary insulin is all that is really needed. Ordinary solution of crystalline insulin should be used in 10 to 20 unit doses (for adults) initially, then repeated about every six hours in amounts determined by results of blood and urine sugar and ketone tests performed four to six hours following each insulin injection. Twenty-four-hour total dosages of 40 to 120 units are sufficient in almost all cases. Overlapping of insulin effect by multiple daily injection, including the night-time hours of sleep, is essential. Depot insulins already in use are better continued than stopped, but should not be relied upon for correction of acidosis. Because of their diurnal variation in intensity of effect it is wise to give intermediate insulins (globin, crystalline-protamine mixtures, NPH, lente) in two equal doses each every 12 hours or so, instead of all of it only once daily.

The usual food supply should be spread out over the entire 24-hour period in fairly uniform feedings. It may then be ignored in interpreting fractional tests. Forty to sixty grams of glucose value every six hours provides an adequate supply and is convenient to administer and ingest. Usually it is given in small meals, lunches, or feedings every three to six hours, night and day. For example, 400 gm. of orange juice or 600 gm. of milk every six hours is a simple method of prescribing and taking it. When indicated it can be given slowly by vein in 5% or 10% solutions of dextrose or by gavage, as milk, cream, egg, and sugar mixtures.

Whenever acidosis is stopped, glycosuria is moderate or absent, and complicating illness is subsiding or past, this regimen should be continued for one to three additional days to establish equilibrium and permit reappraisal of insulin requirements under current conditions. Supplements of insulin can then be given in depot form and food supplies redistributed into meals according to routine custom and rule.

I have described the detailed technique for the use of this method elsewhere.[5,6] Known simply as "six-hour emergency management in diabetes," it was devised by us more than 30 years ago and has been used consistently by many pupils and patients. Duncan has utilized the principles involved in a four-hour modification,[7] but since the peak effect of a single dose of ordinary insulin usually appears at three or four hours in diabetic patients, a urine test at four hours is a little premature. Lags in excretion make it better to empty the bladder at about four hours, test a short collection at five to six hours, and give insulin and food immediately after that test.

Treatment of Severe Acidosis

It should be reemphasized that the more strenous measures to be described in this section are indicated only in clinically symp-

tomatic forms of diabetic acidosis, typically in precomatose and comatose patients who are or have recently been vomiting and dyspneic, are dehydrated, and show high blood ketone and low plasma bicarbonate values.

Insulin.—Far above all other measures in importance, simple solution of crystalline insulin early and in sufficient dosage often will stop ketoacid production and permit repletion of fluids, glycogen, and electrolytes even though nothing else is done. Depot insulins should not be counted on at this time, but should not be stopped. Diagnosis should be accomplished promptly and initial insulin given without delay. It is better to give insulin on suspicion than postpone its use pending definitive laboratory findings. Its action can be covered by glucose administration if later it is found to be excessive, whereas time lost when it is urgently needed cannot be recovered.

The clinical condition, size of the patient, and previous insulin requirement determine the size of initial dosage. The sicker the patient the greater is the need. Young, thin people who have not used large daily doses may react more sensitively than old, fat people who have not been very sensitive to insulin in the past. Infection and trauma increase the need; hypofunctioning thyroid, adrenal, and pituitary states decrease it. Children require less than adults. Deep stupor, marked dyspnea, and severe dehydration call for larger doses, and mild or moderate symptoms, smaller ones.

More specifically, a good rule is to give at least 1 unit per kilogram of body weight in a single subcutaneous dose at once if frank symptoms of acidosis exist, sugar and ketone values are high, and alkali reserve is less than one-half of normal. Much more than this is needed if the patient is desperately sick, if severe infection exists, or if previously smaller amounts have been ineffective. Root reported use of initial three-hour dosages of 71 to 883 units in 213 "coma" cases.[4] Patients with higher admission blood sugar values were given more, and those with lower values, less. Nine out of ten patients in this group with blood sugar values between 200 and 1000 mg. per 100 cc. were given from 99 to 335 units. Corresponding 24-hour cumulative dosages were 151 to 526 units. Root says that about one-half of the first 24-hour requirement is needed within the first 3 hours. It is better to err on the high side than the low.

Initial insulin should be administered in one or two large doses, not multiple small ones. The urgent need is at the outset, not later. It should be given subcutaneously, as a rule, but when circulatory failure or edema are present, one-half should be given by vein to insure absorption and distribution.

Second only to the size of the initial dose is the importance of judging its effect. If dosage has been adequate, unmistakable clinical improvement can be seen three to five hours later. If not, or if the acidosis state worsens in the meantime, much more must be given. The breathless patient responds most dramatically with easier and then normal respiration. A very useful, simple, early sign of insulin effect is rapidly decreasing diuresis as measured hour by hour by use of an indwelling catheter. (This is meaningful only when polyuria has existed and large amounts of sugar are not given concurrently.) Some patients respond with subsiding nausea or restlessness, clearing of the intellect, and slowing pulse.

Quantitative laboratory findings may be of limited value at this stage because results cannot be obtained promptly enough to determine effective action. Urine sugar may decrease abruptly along with diuresis, indicating urgent need for glucose if it has been withheld, as it should be (see below). Blood ketones and sugar show substantial reduction if insulin effect has been decisive. Plasma bicarbonate increases and urine ketones decrease more slowly.

In anticipation of a waning insulin effect after three to five hours (and of a latent period in the response to a second dose), not more than about six hours should elapse before the next injection. If the response to

the first dose has been doubtful or absent, insulin should be given much sooner. When the response has been favorable, however, a six-hour interval is safe. In that event the next dose can be cut to about one-half of the size of the first and each six hours thereafter smaller doses given as long as the symptomatic and laboratory findings are satisfactory. No six-hour dose should be omitted or reduced more rapidly than stated, even after insulin shock. Eventually maintenance requirements are established, a stable 24-hour balance obtained, and depot insulin therapy begun, as described in the previous section.

Fluids.—Three to five liters of fluid should be given to the average adult within the first 24 hours. If shock is present the initial injection should be plasma or whole blood; if not, isotonic saline, M/6 sodium lactate, or a mixture of the two in slightly hypotonic solution. More sodium than chloride is needed. Sudden increases in blood volume should be avoided in older arteriosclerotic patients and others with functional cardiac impairment. Less fluid is required if polyuria is stopped promptly than when it persists due to heavy glycosuria. Excessive glucose administration prolongs glycosuria and inhibits fluid replacement.

When marked oliguria or anuria is present, fluid administration should be reduced sharply, after initial repletion, to not more than total urinary output plus 0.5 to 1 liter daily. Electrolytic and fluid balances then become a special problem.

When vomiting has ceased and coordination recovered, fluid should be given by mouth in the form of water, broth, fruit juice, and milk.

Electrolytes.—Next to insulin and water the greatest need of the patient in severe acidosis is sodium. Thirty to fifty grams is supplied during the first 24 hours by the fluid schedule outlined above; this usually is sufficient.

Potassium depletion is of vital importance and its correction occasionally of life-saving value. Even though serum potassium values at the outset are normal or a little high due to extracellular shifts, a true deficiency exists.[8] This is seen in the uniform and rapid fall in serum potassium coincidently with insulin effect, improved glucose utilization, and intracellular potassium replacement. It is at this point—some 4 to 12 hours after start of treatment—that the hazards of potassium depletion are greatest. Commonly after a short period of improvement they are indicated by intense muscular weakness, including the diaphragm and myocardium, low voltage T-waves in the electrocardiogram, and serum potassium values of 3 mEq. or less.

There are differences of opinion as to the wisdom of using potassium routinely. Probably replacement always is needed, and the amount contained in Ringer's and other similar solutions is of some benefit. These amounts are small, however, and the risk from cardiac standstill is great if larger amounts are used, so most experienced clinicians use potassium by mouth if possible, reserving the intravenous use of it to those patients who show acute deficiency signs. In such cases it should be given in 40 to 80 mEq. amounts at rates not exceeding 20 mEq. hourly. Potassium by vein is particularly dangerous if urine output is low.

Phosphorus deficiency and replacement are comparable to those for potassium. Quantitative data regarding this is lacking, and therapeutic applications are correspondingly uncertain. Administration of potassium as the phosphate salt rather than the chloride is wise.

For elaboration on the use of fluids and electrolytes in the treatment of severe diabetic acidosis the reader is referred to a recent authoritative symposium on the subject.[9]

Sugar.—Practically all observers now agree that glucose should not be given at the outset of treatment. Until insulin action is strong, blood and urine sugar levels are falling rapidly, and water and salt replacement is in process, the use of glucose act-

ually delays recovery. It increases and prolongs diuresis, with consequent heavy loss of water and salts. Repletion is then much more difficult. Dangers from potassium depletion, particularly, are great.

Glucose is not needed until blood and urine glucose levels fall toward or to normal. Then it is needed urgently to forestall insulin shock, which may be severe due to the massive dosage used to stop acid production. Paradoxical as it may seem, having labored to reduce sugar values to normal with insulin it is now good policy to raise them again with administered glucose. Only when glycosuria returns after it has been stopped with insulin can one feel easy about insulin shock.

This type of balance should be maintained until large early insulin doses have been reduced progressively to moderate amounts which need not be feared. Administration may then be stabilized at 40 to 60 gm. amounts of dextrose every six hours by vein, or glucose by mouth as soon as feasible, and sugar-free urine made the objective.

A valid exception to the rule of "no glucose early" is in the presence of marked oliguria or anuria. Frequent urine tests then are meaningless or impossible and insulin effects correspondingly difficult to judge. Under such circumstances constant injection of dextrose by vein in moderate amounts provides a measure of security against unexpected insulin shock. If blood sugar values can be obtained frequently and promptly, this is unnecessary, of course, until they are seen to fall rapidly.

There is increasing evidence that fructose possesses some advantages over glucose in the early treatment of acidosis. Compared, however, with the importance of adequate insulin, fluid and salt replacement, and delay in sugar administration until it is needed, these advantages are not great. Fructose cannot take the place of any of those measures. On the contrary, there are some dangers in its use. Attention may be diverted away from the more essential requirements of insulin, water, and electrolytes. Water loss may be prolonged by excretion of excessive fructose. It can enter the glycolytic cycle without insulin and form liver glycogen, but it leaves the liver as glucose even so.

General.—External warmth, with special precautions to avoid burns, is usually indicated. Gastric evacuation and lavage usually relieves the distress and distention of the dilated stomach. Fluids by mouth are contraindicated, no matter how great the thirst, until normal gastric tone has been reestablished as indicated by hours of freedom from distention and vomiting. The fecal impactions which are so commonly present should be removed by appropriate means.

Except for the use of a liter or two of sodium lactate or bicarbonate at the beginning of treatment, the use of alkali for replacement purposes has been largely abandoned. When acid production is stopped by insulin, alkali reserve will reaccumulate slowly. Acceleration of this process by administration of base does not help much, and deaths from alkalosis have followed too zealous efforts to replace it quickly. Having stopped loss of base with insulin, it is no more necessary to replenish low reserves quickly than to transfuse a patient who has been bleeding after the blood loss is known to have ceased.

Summary

The chief elements in skillful treatment of diabetic acidosis are as follows: (1) prevention by elimination of its common causes in advance; (2) precise diagnosis; (3) correct appraisal of severity; (4) thoughtful and discriminating use of crystalline insulin, with replacement of depleted water and salts, and of sugar later when needed.

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Progress in Internal Medicine

Primary Carcinoma of the Liver

A Clinicopathologic Study of One Hundred Eight Cases

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Primary carcinoma of the liver continues to be a challenging disease, for it is of uncommon occurrence, and it presents a major diagnostic and therapeutic problem. Attention was recently refocused on this disease when it was noted that it had markedly increased in autopsies performed at this hospital during the past decade; the reasons for this increase were analyzed in a previous article from this laboratory, and they will be briefly referred to later. The present study reviews the clinical, pathological, and laboratory features of autopsied cases of primary liver carcinoma at this hospital and contrasts the findings in this series with those of other reports. No attempt has been made to record all previous reports of liver carcinoma, but rather to use the articles dealing either with large numbers of cases, or those dealing with pertinent features of the disease.

Early History

Among the excellent summaries of the historical development of knowledge concerning liver carcinoma were those by Eggel,[1] Sabourin,[2] Winternitz,[3] Counsellor and McIndoe,[4] Steiner,[5] and Berman.[6] Specific reports of cases began when Kelsch and Kiener[7] reported two cases in 1876. Other examples had previously been noted, but they had not been recorded in detail, and in addition there had existed a great confusion concerning primary and secondary liver tumors. The terms hepatoma and cholangioma were introduced by Sabourin in 1881 to differentiate tumors of liver-cell origin from those arising in epithelium of the intrahepatic bile ducts; the terms did not initially gain wide acceptance. By 1901, when Eggel reviewed the literature, he found 162 cases of primary liver carcinoma reported, but only 117 could be accepted, for a critical differentiation had not been made between primary and secondary tumors. In 1911 Yamagiwa[8] reintroduced the terms hepatoma and cholangioma, and they have since been in general use. As of 1951 Berman stated that over 2000 cases of primary liver carcinoma had been reported in the world literature.

Material and Methods

The material upon which this study is based consists of 108 autopsied cases of primary liver carcinoma occurring among 23,114 autopsies at the Boston City Hospital during the years 1917 through 1954. The gross and microscopic records of all cases were reviewed. Microscopic sections of the liver tumors were studied in 47 of 80 cases of hepatoma, in 4 cases of hepatocholangioma, and in 15 of 24 cases of cholangioma. The remaining cases were accepted as valid from a review of the gross and microscopic descriptions made at the time of autopsy.

All cases of the seven types of cirrhosis as diagnosed microscopically at this laboratory among autopsies during the years 1917 through 1954 were tabulated in order to determine the incidence of carcinoma in each type of cirrhosis. The frequency with which liver carcinoma was clinically diagnosed in each of the three main types of cirrhosis in which carcinoma occurred was determined and was compared with actual occurrence at autopsy. This tabulation was made from autopsy records of each type of cirrhosis, comparing the findings with the diagnoses sent to the pathologist

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in the clinical summary of each case. For this purpose a random sample of the following types of cirrhosis was used: 400 cases of fatty nutritional cirrhosis (alcoholic cirrhosis, portal cirrhosis, Laennec's cirrhosis), 177 cases of healed acute yellow atrophy (toxic cirrhosis, postnecrotic cirrhosis), and 124 cases of hemochromatosis.

As will be noted later, liver carcinoma was frequently complicated by bleeding from esophageal varices and peptic ulcers and by intraperitoneal hemorrhage. For comparison with these cases, the frequency with which fatty nutritional cirrhosis, healed acute yellow atrophy, and hemochromatosis were complicated by these three conditions was determined. A total of 500 cases of cirrhosis without tumor was reviewed for this purpose, using consecutive cases from the most recent years.

The clinical and laboratory records of 57 cases of hepatoma and of 15 cases of cholangioma were available and were reviewed. These were chiefly from the years 1940 through 1954.

Results

General

Incidence.—The occurrence of 108 cases of liver carcinoma in 23,114 autopsies was an incidence of 0.47%. The incidence in autopsies increased in recent years as mentioned earlier, from 0.34% in 15,491 autopsies during the years 1917 through 1946 to 0.72% in 7623 autopsies during the years 1947 through 1954. The reasons for this increase, as set forth previously,[9] were chiefly considered to be three in number: an increase in number of cases of healed acute yellow atrophy and of fatty nutritional cirrhosis, both of which types of cirrhosis were accompanied by a proportional increase in number of cases of liver carcinoma, and an increase in number of cases of liver carcinoma occurring in adults without underlying cirrhosis. Certain other workers have noted an unusually high incidence of liver carcinoma in recent years,[10-12] while still other recent reports[13] have failed to call attention to such an increase. Berman summarized 20 reports from North America up to 1943 as averaging 0.27% in 108,632 autopsies.

Age.—The average age of all patients in this series was 64 years. Excluding two children, 20 months and 16 years of age, the average age for the group with hepatoma was 63 years, while that for the group with cholangioma was 67 years. The predominant age range was 50 to 79, with the greatest number, 53, occurring between the years 60 to 69. The average age in this series was higher than for most reports in the literature and may be a reflection of the older age population at this hospital, although increased longevity of recent years may also be a factor. Greene,[14] in a collective review of 386 cases, found the greatest incidence during the years 50 to 59. Gustafson,[15] in 62 cases, found an average age of 52.5 years, while two recent reports[16,17] found average ages of 57 and 60 years.

Race.—Of the 108 patients 98 were of Caucasian extraction; 5 were Chinese, all males, and 5 were Negroes, all males. There was one Chinese male with cholangioma and one Negro male with cholangioma, the remainder of Chinese and Negroes having hepatoma. This number of Chinese patients with liver carcinoma is quite high, inasmuch as only 83 Chinese patients were autopsied at this hospital during the 38 years of this study, compared with 2010 Negroes and 21,021 Caucasians. Other reports of racial incidence have agreed that Chinese patients, even those living in North America[18] have a higher incidence of liver carcinoma than the comparable white population. Many authors[19] have speculated that this higher incidence is due to preexisting parasitic liver disease. There was no evidence in this group of patients to support such an underlying cause, and it is possible that other factors, such as diet and malnutrition, should be considered.

Sex.—Eighty-eight patients were males and 20 were females; in the group of 84 hepatomas there were 75 males and 9 females, while of the 24 patients with cholangioma 13 were males and 11 were females. A similar sex difference has been noted by other workers; the predominance of males in this series (81% of the total) agrees with most reports. Greene found 86% of 386 patients to be males and 14%, females.

The ratio of males to females in 230 patients in 7 other reports was 87% to 13%.[15-17,20-23]

Clinical

The clinical data of this study are presented in the order in which they usually become available to the clinician, namely, the features of the history, the physical examination, and the laboratory data.

Types of Cirrhosis.—In the 72 cases clinically reviewed the following types of cirrhosis were present: 21 fatty nutritional cirrhosis, 20 healed acute yellow atrophy, 6 hemochromatosis, 4 undetermined type cirrhosis, 4 biliary cirrhosis, and 17 with no underlying cirrhosis.

Chief Complaint.—The principal complaints which led the patients in this series to seek hospital admission could be grouped under three general headings. The largest number, 41 (57% of the 72), complained of pain or abdominal discomfort. In 33 patients the pain was only moderate, abdominal in location, usually in the right upper quadrant or in the epigastrium, although diffuse abdominal pain was not unusual. In eight patients it was located in the low back or over the right shoulder or scapula. Back pain was particularly prominent because of its severity and persistence in the patients with cholangioma. The next commonest complaint, in 13 patients, was weakness and weight loss, leading the examiners to suspect the presence of neoplasm. The third group, 11 in number, was that of patients complaining of abdominal and leg swelling of recent and rather rapid onset. In such patients the picture was that of rapidly decompensating liver disease, usually considered to be on a cirrhotic basis. The remaining complaints were rectal bleeding in two cases, recent onset of confusion and disorientation in two cases, and constipation, vomiting, and painless jaundice each in one case.

Pain, usually abdominal, has been a prominent symptom in most reports. In 846 cases reported by 12 authors [4,12-21,23] it was present in 323 cases, or in 38.2%. Some authors list other symptoms as commoner. Tull [19] found weakness in 89% of 134 cases, and Hoyne and Kernohan [21] found weakness and abdominal distention in 87% of 31 patients.

Duration of Symptoms.—The clinical course of liver carcinoma has generally been noted to be short. The duration of presenting symptoms before admission for 71 of the patients in this series was as follows: 27 less than 1 month, 10 from 1 to 2 months, 16 from 2 to 4 months, 10 from 4 to 6 months, 2 from 6 to 10 months, and 6 longer than 11 months. The longest period of continuing symptoms was two and one-half years, although in this case the presence of tumor was not established on an anatomical basis at the time of onset of symptoms. Five other patients had consistent symptoms, usually pain, for one year. Many authors cite length of clinical course as approximately three months,[15,17] which is consistent with the findings in this series. Exceptions of long survival after the time of diagnosis have occasionally been noted.

Hypoglycemia.—One of the patients with liver-cell carcinoma presented an unusual clinical problem of recurring episodes of marked hypoglycemia, which led to a clinical diagnosis of islet-cell tumor of the pancreas. The patient was a 36-year-old white man with healed acute yellow atrophy and with replacement of nearly the entire right lobe of the liver by tumor. Metastases were present in regional lymph nodes and in the lungs. His duration of symptoms before hospitalization was three months, during which time he complained of vague abdominal pains. His hospital admission was precipitated by extreme weakness, related to hypoglycemia. He died after two weeks in the hospital, with an unsuspected bleeding duodenal ulcer. Similar cases of marked hypoglycemia have been reported,[24-27] but they appear to be extremely rare.

Jaundice.—The presence or absence of jaundice was determined in this series only in the 72 patients whose clinical and laboratory records were reviewed. Jaundice was present in 37 cases (51.4%); it was only

slight in 19 patients and marked in the remaining 18 patients. In the cases with jaundice of slight degree the icteric index ranged from 15 to 40 units. The icteric index in the 18 patients with deep jaundice ranged from 60 to over 100 units. There was no difference in incidence or degree of jaundice between patients with hepatoma as compared to those with cholangioma. Jaundice was usually progressive during the hospital course, and, as noted by most other workers, it was of the obstructive type. It is of interest that in the group with mild jaundice the initial examiner often did not find jaundice until a slightly elevated icteric index was reported. In 924 cases reported by 13 authors [6,11-17,19-21,23,28] jaundice occurred in 438 cases, or in 47.4%.

Ascites.—The presence of ascites was determined in this series from the findings at autopsy, this being the most reliable method of establishing its presence. Of the 108 patients, 72 (66.6%) had ascites at autopsy. In 23 cases it was bloody or blood-tinged fluid (21.3% of the 108 patients). Patients with tumor involvement of the portal, hepatic, and inferior vena caval veins did not have a higher incidence of either ascities or bloody ascites than did patients without such involvement. This is in contrast to the experience of some other workers.[13] In two remarkable cases, one with complete thrombosis of the portal vein, the other with complete thrombosis of the inferior vena cava, neither had ascites. The occurrence of ascites in 529 cases reported by 11 other authors [6,11-13,15-17,19-21,23] was noted in 296 cases, or 56%. The frequency with which bloody or blood-tinged ascitic fluid has been found has been in general agreement. Spatt and Grayzel,[17] found this in 17.6% of 17 cases; Hoyne and Kernohan,[21] in 22.6% of 31 cases, and Tull,[19] in 33.6% of 134 cases.

Size and Tenderness of Liver.—A large liver was found clinically in 30 of 72 patients (41.7%), which correlated surprisingly well with necropsy findings, in view of the frequency with which ascites was present. Only four patients had a rapidly enlarging liver mass while in the hospital. At autopsy the average liver weight, excluding the two children in this series, was 2260 gm. Three livers were less than 1000 gm., weighing 560, 760, and 800 gm. Eighteen were between 1001 and 1500 gm.; thirty-seven, between 1501 and 2000 gm., and twenty-three, between 2001 and 2500 gm. The remainder were over 2500 gm.; the livers of the four patients with rapidly enlarging right upper quadrant masses weighed 5400, 5400, 5440, and 5560 gm.

General abdominal tenderness was present in 8 patients, while epigastric and right-upper-quadrant tenderness were present in 27 cases, an occurrence of abdominal tenderness in 48.6% of the 72 patients.

Spleen.—An enlarged spleen was noted clinically in only three cases. At autopsy the average splenic weight was 306 gm. The cases in which tumor invaded large regional veins did not differ in splenic size from the cases without such invasion. Thus the average weight in the former group was 318 gm., while that of the latter group was 300 gm. The largest spleen encountered was 1190 gm., in a patient with portal vein invasion, with an undetermined type cirrhosis, and without esophageal varices. The next largest spleen was 1130 gm., in a patient without large-vein invasion, with portal type cirrhosis, and with intact esophageal varices at autopsy. One patient with complete tumor thrombosis of the portal vein and another with complete thrombosis of the inferior vena cava had spleens weighing only 30 and 90 gm.

Fever.—The presence of fever in liver carcinoma has been denied by some authors or said to be only terminal in occurrence,[14,19] while others have noted the presence of fever, usually of slight degree. Thus Hoyne and Kernohan [21] found fever in 38.7% of 31 cases; Spatt and Grayzel,[17] in 64% of 17 cases; Smith,[20] in 44% of 25 cases; Gustafson,[15] in 47% of 62 cases, and Berman,[6] in 38% of 75 cases. Of 72 cases reviewed clinically in this series, 19 had

temperatures between 98 and 102 degrees F, and an additional 22 patients had temperatures between 97 and 99 degrees F, an occurrence of fever, including the latter group, in 41 of the 72 patients, or in 56.9%. The character of the temperature elevations was considered to be a noteworthy feature. Daily afternoon elevations from a normal or subnormal level were almost invariably present in those patients with fever. Similar temperature rises are often seen in inflammatory, infectious, and neoplastic diseases, but this finding is considered to be of some value in determining that cirrhosis is complicated by another process.

Hospital Course.—The hospital course of most patients before death was less than four weeks. Of 72 patients the course of 21 was less than one week; of 14, was one to two weeks; of 29, was two to four weeks, and of 8, was four to eight weeks. Tull,[19] in his study of 134 patients, noted that the average interval from admission to death was two weeks.

Accuracy of Clinical Diagnosis.—The well-known difficulty of establishing the clinical diagnosis of liver carcinoma was borne out in the present study. Of the 108 cases in this series, the correct diagnosis was made clinically 20 times, or in 18.5% of cases. In seven of these cases the diagnosis had been made by laparotomy and surgical biopsy of the liver. The diagnoses most often considered were metastatic tumor involving the liver and neoplasm of some other portion of the biliary system. These latter two diagnoses were made in 36% of cases.

The frequency with which the diagnosis of liver carcinoma was entertained in patients with cirrhosis is of interest. In 400 patients with fatty nutritional cirrhosis primary liver tumor was considered 16 times, or in 4% of cases. Only one of this number had such tumor at autopsy. The diagnosis of primary liver tumor, then, was considered in patients with fatty nutritional cirrhosis in 4% of cases, as compared with an actual rate of occurrence in this series, as will be seen later, of 2.4%. In the 177 autopsy records of patients with healed acute yellow atrophy reviewed for this purpose there occurred 26 cases of primary liver tumor, 2 of which were correctly diagnosed clinically. The clinical diagnosis of liver carcinoma was entertained in the entire group five times, or in 2.8% of cases. This is contrasted with an actual rate of occurrence of liver carcinoma in this type of cirrhosis of 13.1%. In the group of 124 cases of hemochromatosis liver carcinoma was considered 6 times, or in 4.6% of cases; two of these diagnoses proved to be correct. The actual rate of occurrence of liver carcinoma in hemochromatosis was 7.7% in this series.

It is of passing interest to note that only 15 of the 124 patients with hemochromatosis were correctly diagnosed clinically as having that disease. In 22 other patients of this group the diagnosis of another type of cirrhosis was made, so that the remaining 72 patients came to autopsy without a diagnosis of liver disease, despite the finding at autopsy that all 72 had liver involvement, usually a well-marked pigment cirrhosis. This failure of clinical diagnosis was generally due to the absence of what are usually considered to be the classical features of the disease: diabetes, bronzing of the skin, and clinical liver disease. Inasmuch as hemochromatosis is often thought to be one of the more clinically obvious types of liver disease, some difficulties of diagnosis confronting the clinician are emphasized.

Laboratory Data

The laboratory determinations in this series that gave the most helpful information were the serum icteric index, the urine bile test, the serum sulfobromophthalein (Bromsulphalein) retention, the prothrombin time, the serum albumin-globulin ratio, and the serum alkaline phosphatase.

Routine Blood Tests.—The routine blood tests gave little information of diagnostic value. Many patients in this series had bleeding complications due to esophageal varices and peptic ulcers, as will be detailed

later; as a result, the finding of anemia was common. Hematocrits were performed in 38 patients; they averaged 35%, with 18 of the 38 values less than 35%. Thirty-one of the remaining patients had blood hemoglobin values determined, the average of these being 79% of normal. The white blood cell counts were usually normal, some were high, and occasional counts were low. Three of the patients had persistent eosinophilia. One patient with persistent differential counts containing 20% eosinophiles was a 76-year-old white man with an undetermined type of cirrhosis and a hepatoma that had spread to regional lymph nodes and was invading the portal vein. Another patient with 32% eosinophilia was a 36-year-old white man without underlying cirrhosis, with a hepatoma that had spread to regional lymph nodes and to lungs. The third patient was a 71-year-old white man with eosinophile differential counts averaging 60%. He had hepatoma arising in a liver with fatty nutritional cirrhosis, and no tumor metastases were present. Only two factors were present in all three patients: they were all men and they all had tumor of the liver-cell type. Most other workers have found some anemia in their cases, and persistent eosinophilia has been found occasionally.[11,12]

Urine.—The single urine examination that proved to be of value was the test for the presence of bile. This was performed in 57 patients and was positive in 35 (61.4%). The presence of urine bile appeared to be a reflection of jaundice of the obstructive type. The value of the test was that it was positive in eight patients in whom clinical jaundice had not been noted initially but whose icteric indices were slightly elevated and in whom definite jaundice developed during the hospital stay. Urine urobilinogen tests were performed frequently and were usually normal.

Sulfobromophthalein Retention. — This test was performed in 23 cases and was reported in per cent retention after 45 minutes. All but one of the values were abnormal. The highest value was 83%; the lowest, 2%, and the average was 41%. Eight values were 50% or greater, 5 were 20% to 29%, and 5 were 30% to 39%. Schupbach and Chappell [12] and Spatt and Grayzel [17] noted the sulfobromophthalein test to be one of the most consistently altered tests in primary liver carcinoma.

Prothrombin Time.—This test was performed in 37 patients. The value in seconds was compared with a normal control and was then converted, for purposes of this report, into per cent of the normal control value. All but four of the values were abnormal, the average being 66% of normal; 18 values were less than 70% of normal.

Alkaline Phosphatase. — This test was done in 21 cases and was reported in Bodansky units. Four of the values were normal, seventeen were elevated, but four of these seventeen only slightly so. The lowest value was 2.4 units, the highest 29 units, and the average 8.9 units. Ten values were between 4.6 and 9.4 units, and six were above 9.4 units, all but one of the latter falling in the range 10 to 15 units. In nearly all reviews of large numbers of cases of liver carcinoma the alkaline phosphatase test has been performed only occasionally, hence little information from similar studies has been available. In seven of the cases reported by Spatt and Grayzel [17] the alkaline phosphatase values averaged 16.9 Bodansky units.

Total Protein and Albumin-Globulin Ratio.—The total serum protein was determined in 42 patients; the highest value was 10.3 gm. per 100 cc.; the lowest, 4.3 gm. per 100 cc., and the average, 6.4 gm. per 100 cc. Nineteen values fell between 5.5 and 6.5 gm. per 100 cc. and 12 between 6.6 and 7.5 gm. per 100 cc. The serum albumin-globulin ratio was determined in 30 patients; it was reversed in 21 and normal in 9. Other reports [17] have noted that the total serum protein values are not consistently altered in liver carcinoma. Schupbach and Chappell [12] noted that the albumin-globulin ratio was one of the most constantly altered liver function tests.

Cephalin Flocculation and Formol Gel.—The cephalin flocculation test has been noted to be inconsistent in liver carcinoma.[17] The test was performed in 38 patients in this series and was abnormal in 28 (73.7%) and normal in 10 patients. The degree of flocculation was variable. The formol gel test was performed in 22 cases; it was abnormal in 14 and normal in 8. In general positive formol gel tests corresponded to a reversed albumin-globulin ratio, for which the test is often used as a rapid and simple method of detecting such a reversed ratio. In three patients, however, with normal albumin-globulin ratios the formol gel tests mine whether these results were due to the presence of an abnormal globulin fraction, although this appeared to be a possible were positive. There was no way to deter- explanation.

X-Ray Diagnosis.—In this series routine radiologic methods did not contribute to diagnosis. A high diaphragm on chest x-ray and displacement of the duodenum on abdominal film or gastrointestinal series was occasionally noted, but their significance was not appreciated at the time. Schatzki[29] has discussed roentgenologic criteria for diagnosing liver carcinoma. These consist of evidence of cirrhosis; esophageal varices; a mass in the region of the liver displacing stomach, duodenum, colon, and occasionally the small intestine; positive evidence of metastases, particularly in the lungs, and a localized bulge of the diaphragm.

Examination of Ascitic Fluid.—The ascitic fluid from 11 of 72 patients was examined for the presence of tumor cells as an aid to clinical diagnosis; all the tests were negative. Of those cases where the examination was made, three patients had no extrahepatic metastases; three had invasion of portal, hepatic, or inferior vena caval veins; three had lung metastases, and two had intra-abdominal metastases, the latter, however, confined to lymph nodes. In one case with lung metastases examination of the pleural fluid was also negative for tumor cells. Other workers have noted a similar unsatisfactory result with this test. Loesch[22] reported that in 6 of 14 patients with cell block examinations of the ascitic fluid, all were negative. Holley and Pierson[11] found the test unsatisfactory in 3 of 5 patients in whom it was performed.

Liver Biopsy.—Needle biopsy of the liver was performed in 5 patients, giving a correct diagnosis in only 2 cases. In the remaining 3 patients an inadequate sample of liver tissue was obtained in one, and normal liver tissue was obtained in the remaining two. By contrast, in 7 other patients in whom surgical liver biopsy was obtained at time of laparotomy, the correct diagnosis was made in all cases. This difference of results between the two methods is obviously due to a better selection of a biopsy site at laparotomy. Sanford[16] noted that in two of his cases needle biopsy of the liver showed adenocarcinoma in both, one of which was interpreted as possibly arising in the lung, and the other as of unknown primary origin. Loesch[22] noted that in eight patients having liver biopsy, five by the needle method and three at laparotomy, all showed carcinoma, four of which were identified as primary in the liver. Hoyne and Kernohan[21] noted that in eight patients whose livers were biopsied at laparotomy all showed tumor.

Therapy

No significant information concerning the more aggressive forms of therapy was obtained from a study of the cases in this series. Radiology was not used as a form of therapy, and in those cases where laparotomy was performed no attempt at definitive surgery was made. The poor prognosis with supportive and conservative forms of therapy is apparent, however, from the generally short and progressive downhill course of nearly all patients so treated in this and in other series of cases. The medical literature does not contain hopeful information concerning radiological or surgical treatment. Two reports of x-ray therapy that were reviewed[31,32] gave only equivocal results. Among the more than 2000 cases of liver

carcinoma in the literature there are relatively few reports of surgically treated cases.[33-54] Although survival for as long as nine years has been recorded following surgery,[36] the majority of patients in such reports were dead within less than five years. Most reports of surgical attempts at cure were made in earlier years, before the development of newer surgical aids, and it remains to be seen whether current attempts at surgery will be more successful.

Pathology

Carcinoma and Cirrhosis.—Of the 108 tumors in this series 82, or 76.9%, were associated with cirrhosis. A difference between hepatoma and cholangioma was observed: Of the 84 hepatomas 72, or 85.7%, were associated with cirrhosis, while only 10 of the 24 cholangiomas, or 41.7%, were associated with cirrhosis. The incidence of carcinoma in all types of cirrhosis was 3.4%; as shown in Table 1 there were differences in the incidence of tumor in the various types of cirrhosis. Healed acute yellow atrophy and hemochromatosis were associated with liver carcinoma with far greater frequency, 13.1% in healed acute yellow atrophy and 7.7% in hemochromatosis, than any of the other types of cirrhosis. In most prior writings the high association of liver carcinoma with hemochromatosis has been commented upon. Berk and Lieber,[55] in a review of 1989 cases of cirrhosis in the literature, chiefly found primary carcinoma in 90 cases, or in 4.5%, while carcinoma associated with hemochromatosis occurred 32 times in 436 cases, an incidence of 7.3%. The high incidence of liver carcinoma in healed acute yellow atrophy at this hospital was commented upon in an earlier report.[9]

TABLE 1.—*The Occurrence of Primary Liver Carcinoma in Seven Types of Cirrhosis*

Type of Cirrhosis	No. with Cirrhosis	No. with Carcinoma	Per Cent with Cirrhosis
ealed acute yellow Hatrophy	222*	29†	13.1
Hemochromatosis	155‡	12§	7.7
Fatty nutritional	1,099	26	2.4
Undetermined type	378	8	2.1
Biliary	340 ‖	7	2.1
Cardiac	202	0	0
Syphilitic	36	0	0
Total	2,402	82	3.4

*In 28 cases fatty nutritional cirrhosis was also present.
†In 1 case fatty nutritional cirrhosis was also present.
‡In 15 cases fatty nutritional cirrhosis was also present.
§In 2 cases fatty nutritional cirrhosis was also present.
‖ In 10 cases fatty nutritional cirrhosis was also present.

An association of liver carcinoma with cirrhosis is generally well documented, and the difference in the figures for hepatoma and cholangioma noted in this series are in agreement with most reports. Greene[14] found 87% of hepatomas and 37% of cholangiomas to be associated with cirrhosis; Hoyne and Kernohan[21] found 75% of hepatomas and 18% of cholangiomas with such an association, and Gustafson[15] found this association in 64% of hepatomas and 33% of cholangiomas. Berman[6] summarized 893 cases of liver carcinoma reported by 28 authors and found cirrhosis in 67.2% of cases. Both Berman and Tull,[19] however, in reporting from South Africa and Singapore, respectively, found higher associations of cirrhosis and cholangiomas than most authors have reported. In Tull's cases 76% of hepatomas and 66% of cholangiomas occurred in cirrhotic livers, while all of Berman's cases that were studied histologically, (60 of a total of 75) showed underlying portal cirrhosis. Four of these 60 tumors were cholangiomas, and the remainder were hepatomas.

Gross Types of Carcinoma.—Using the gross classification proposed by Eggel,[1] the tumors of this series were classified from gross descriptions and measurements made at autopsy as nodular in type if there were discrete nodules varying from a few millimeters to several centimeters in diameter; massive in type if one large mass occupied an entire lobe, often with satellite nodules at its periphery, and diffuse in type if the tumor was grossly infiltrative and indistinguishable from cirrhosis. Ninety-two of the tumors were nodular in type, and sixteen were massive in type; there were no cases of the diffuse type. The massive type was found only in cases of hepatoma.

Microscopic Types of Carcinoma.—Of the 108 tumors, 80 were hepatomas, 4 were hepatocholangiomas, and 24 were cholangiomas. The four hepatocholangiomas contained chiefly hepatocellular elements, and for purposes of discussion in this report are generally included with the hepatomas. It is not the purpose of this study to take up the histological aspects of these tumors in detail; the reports of Berman [6] and of Edmondson and Steiner [13] discuss the microscopic features at some length, and little can be added from the present series of cases. In early reports of liver carcinoma the incidence of cholangioma was extremely high, whereas most workers now agree that hepatoma is commoner than cholangioma. This difference in early and later cell types has been ascribed to more definite histologic criteria of recent years. Of 549 cases in 11 other reports, 420, or 76.5%, were hepatomas; 116, or 21.1%, were cholangiomas, and 13, or 2.4%, were hepatocholangiomas. [11-13,15-17,19-23]

Metastases.—Spread to various organs was common in this series, in both hepatomas and cholangiomas, and is summarized in Table 2. Involvement of organs other than the liver was found in 75% of hepatomas and 59% of cholangiomas. Other than regional lymph nodes, the area most often involved by metastasis was the lungs (36.9% of hepatomas, 41.7% of cholangiomas), followed by intra-abdominal organs and distant lymph nodes, the latter usually mediastinal and para-aortic in location. Lung metastases were usually small in size and located in the periphery of the lungs. Bone metastases involved the vertebral column three times, causing paraplegia in one instance; the ribs twice, and the humerus one time. Involvement of the heart in three cases was by growth along the inferior vena cava and into the right auricle. In one instance tumor had grown as far as the right ventricle. One striking feature of hepatomas was their tendency to invade large veins, particularly the portal and hepatic veins, often with growth within adjoining large vessels for a considerable distance. Forty of the eighty-four hepatomas (47.6%) and three of the twenty-four cholangiomas (12.5%) showed such large vessel invasion. The incidence of metastases in this series is in general agreement with prior reports. Wilbur and co-workers [23] found extrahepatic metastases in 53% of cases; Hoyne and Kernohan,[21] in 68% of cases; Berman,[6] in 60% of cases. Greene,[14] in reviewing 386 cases, found that 31% had spread to regional lymph nodes and 28% to lungs. In 10 reports [6,12,15-17,19-23] 158 of 437 cases, or 36.2%, involved the lungs. Invasion of large veins was noted in Greene's review in 18% of cases, and in 456 cases reported by eight authors [13,15-17,19,20,23,56] such growth was found 123 times, or in 27% of cases.

TABLE 2.—*The Sites of Spread of 77 of a Total of 108 Primary Liver Carcinomas having Metastases*

	Extrahepatic Spread	Regional Vessels or Nodes Only	Distant Organ Involvement
Hepatomas (84 cases)	63	26	37
Cholangiomas (24 cases)	14	1	13
	77	27	50

Distant Organs Involved in 50 Cases

	Hepatomas (84 cases)	Cholangiomas (24 cases)	Totals
Lungs	31	10	41
Abdominal organs	10	6	16
Distant nodes	10	6	16
Diaphragm	5	1	6
Adrenals	4	2	6
Bone	3	1	4
Kidneys	1	3	4
Heart	2	1	3
Brain	2	0	2

Bleeding Complications.—One of the striking findings in this series was the frequency with which bleeding complications occurred; these were due to esophageal varices, gastric and duodenal ulcers, and intraperitoneal hemorrhage. Table 3 summarizes these complications. Bleeding esophageal varices were found 17 times in the 108 cases (15.7%), bleeding ulcers 5 times (4.6%), and intraperitoneal hemorrhage 5 times (4.6%), an incidence of hemorrhage in the entire group of 25%. In addition, intact varices and nonbleeding ulcers were found in another 18.5% of

TABLE 3.—*Esophageal Varices, Peptic Ulcers, and Intraperitoneal Hemorrhage in 47 of a Total of 108 Patients with Primary Liver Carcinoma*

	Varices	Ulcers	Intra-peritoneal Hemorrhage	Totals
Hepatomas (84 cases)				
Intact	18	6	--	24
Bleeding	16	5	4	25
Cholangiomas (24 cases)				
Intact	1	1	--	2
Bleeding	1	0	1	2
Totals	36	12	5	53*

*Six patients had two of the complications shown in the Table.

cases. Excluding 6 instances shown in Table 3 because 6 patients had two of the complications shown, 44 of 84 patients with hepatoma, or 52.4%, had varices, ulcers, or intraperitoneal hemorrhage, while 25 of the 84 patients with hepatoma, or 29.8%, had severe hemorrhage from these sites. This contrasts with the 24 patients with cholangioma, of whom 3, or 12.5%, had one or more of these three bleeding complications, and only one, or 4.2%, had severe hemorrhage. The prothrombin time was determined in 10 of the patients with bleeding esophageal varices, and it averaged 74% of normal. In five patients with bleeding peptic ulcers it averaged 49% of normal.

Fatal hemorrhage has been noted with varying frequency in the reports in the literature dealing with liver carcinoma. Nine of thirty-eight patients (23.7%) reported by Sanford [16] had exsanguination, four from esophageal varices and five from intraperitoneal hemorrhage. Strong, Pitts, and McPhee [30] noted that 14 of 55 patients (24.5%) died as the result of the bleeding complications of ruptured esophageal varices or intraperitoneal hemorrhage. Wilbur and co-workers [23] reported terminating bleeding in 15 of 49 patients (30.6%), 2 of whom had ruptured esophageal varices; 1, recurrent epistaxis, and 12, intraperitoneal hemorrhage. Edmondson and Steiner [13] reported that 13 of 75 patients with hepatoma and 1 of 18 patients with cholangioma had terminating bleeding from esophageal varices, an incidence of 15.1%. By contrast, Berman [6] noted this only twice in 75 cases, and Tull [19] did not find it in any instance in 134 cases. It is possibly of importance in this connection that the patients in both Tull's and Berman's reports were chiefly young adults, in contrast to middle-aged and elderly patients with liver carcinoma in most other series of cases.

The occurrence of bleeding complications in three types of cirrhosis, uncomplicated by liver carcinoma, is shown in Table 4.

TABLE 4.—*Esophageal Varices, Peptic Ulcers, and Intraperitoneal Hemorrhage in 500 Cases of Cirrhosis Not Complicated by Liver Carcinoma*

	Varices	Ulcers	Intra-peritoneal Hemorrhage	Totals
Fatty nutritional cirrhosis (250 cases)				
Intact	66	9	--	75
Bleeding	31	3	2	36
Healed acute yellow atrophy (150 cases)				
Intact	40	2	--	42
Bleeding	21	1	1	23
Hemochromatosis (100 cases)				
Intact	11	4	--	15
Bleeding	5	1	0	6
Totals	174	20	3	197

Bleeding varices, ulcers, and intraperitoneal hemorrhage occurred in fatty nutritional cirrhosis in 14.4% of 250 cases, in healed acute yellow atrophy in 15.3% of 150 cases, and in hemochromatosis in 6% of 100 cases. The incidence of bleeding complications in liver carcinomas in this series, particularly hepatomas, is somewhat greater than in uncomplicated cirrhosis, inasmuch as a large number of cases of liver carcinomas occurred in patients without cirrhosis and in patients with types of cirrhosis that are not accompanied by a high incidence of varices, ulcers, or intraperitoneal hemorrhage. The occurrence of intact varices and nonbleeding ulcers, however, was not greater in patients with liver carcinoma than in patients with uncomplicated cirrhosis.

Causes of Death.—In most reports of liver carcinoma the immediate causes of death are not given in detail. In the present study these were determined in 82 cases where adequate clinical as well as autopsy

TABLE 5.—*Immediate Causes of Death in 82 of a Total of 108 Patients with Liver Carcinoma*

Bleeding from varices, ulcers, or intraperitoneal hemorrhage	26
Liver coma	25
Pneumonia	10
Cachexia	4
Atalectasis	4
Cerebral vascular accident	4
Pulmonary emboli	3
Congestive heart failure	3
Acute myocardial infarction	1
Subdiaphragmatic abscess	1
Empyema of the gallbladder	1
	82

information was available; the results are summarized in Table 5. The three main groups of conditions causing death were (1) hemorrhage from ruptured esophageal varices, bleeding peptic ulcers, or intraperitoneal hemorrhage due to rupture of a tumor nodule on the surface of the liver or due to erosion of a large vein; (2) liver coma, and (3) the complications of weakness and confinement to bed, which were pneumonia, atalectasis, and pulmonary emboli arising from leg-vein thrombi.

Comment

Certain findings in this series of cases differed from those of other reports; two of the most striking features were the increase in incidence of liver carcinoma in autopsies at this hospital during the past decade and the high occurrence of liver carcinoma in healed acute yellow atrophy. The reasons for the recent increase in cases of liver carcinoma were discussed in an earlier article. Attention was directed there to the finding of liver carcinoma as one of the sequelae of healed acute yellow atrophy and to the roles of infectious and homologous serum jaundice and of malnutrition in the development of this type of cirrhosis; to an increase in cases of fatty nutritional cirrhosis in which potent alcoholic beverages appeared to be implicated, and to an increase in the number of cases of liver carcinoma developing in adults without cirrhosis. The frequency with which liver carcinoma occurred in healed acute yellow atrophy, 13.1%, exceeded even that of hemochromatosis, in which the incidence of carcinoma was 7.7%. In an earlier report from this hospital covering the years 1897 to 1932 the occurrence of liver carcinoma in healed acute yellow atrophy was 6.5%, while that of hemochromatosis was 8.2%.[57]

Another feature of the present series of cases to which attention is directed is the frequency with which bleeding complications due to the presence of esophageal varices, peptic ulcers, usually of the duodenum, and intraperitoneal hemorrhage terminated the lives of patients with liver carcinoma.

Despite the continuing attention that has been given to primary liver tumors during the past 80 or more years, the disease remains one of the most difficult to diagnose clinically, and there has not been evolved any significant form of therapy. The findings in this series support the often made statement that there is no diagnostic clinical picture. From this series the features which may lead the clinician to strongly suspect the diagnosis include the following: 1. A man over the age of 35 years, often with cirrhosis; 2. complaints of vague abdominal pain, usually located in the right upper quadrant and of relatively recent onset; or complaints of rapidly accumulating abdominal and leg fluid, again of recent onset, the latter giving the impression of rapidly decompensating liver disease in a patient with known cirrhosis; 3. a palpable liver or a mass in the right upper quadrant, often with diffuse abdominal tenderness, more marked in the right upper quadrant; 4. jaundice, usually of mild degree; 5. ascites, often blood-tinged; 6. an unexplained low-grade fever, with late afternoon elevations; 7. no other demonstrable site of primary tumor for liver metastases; 8. radiologic findings of a large liver, often with a mass displacing the stomach and duodenum, esophageal varices, an elevated region of the diaphragm, and tumor metastases in the lungs, as a late finding; 9. laboratory findings of a slightly elevated icteric index, a positive urine test for the presence of bile, a markedly elevated sulfobromophthalein retention test, a lengthened prothrombin time, a reversed albumin-globulin ratio, and an elevated serum

alkaline phosphatase. It bears emphasis that the finding of one or more negative laboratory examinations does not exclude the diagnosis of liver carcinoma. Little weight should be given to a negative examination of the ascitic fluid for tumor cells if other evidence points to the diagnosis. Also, a negative needle biopsy of the liver does not eliminate this diagnosis when it is otherwise indicated.

There is, at the present time, no specific form of therapy that may be advocated. The known hopeless outcome resulting with conservative therapy may encourage more aggressive attempts, particularly surgery. This would offer the best chance for cure when the disease is found early, before intrahepatic spread has occurred. Next to the discovery of more specific etiologic and therapeutic agents for all types of neplasms, attention in liver carcinoma should also be directed to preventing the underlying condition of cirrhosis.

Summary and Conclusions

A study of 108 autopsied cases of primary liver carcinoma occurring at the Boston City Hospital during the years 1917 through 1954 is presented, and a comparison is made between the findings in this and other reported series of cases.

Attention is called to the fact that primary liver carcinoma increased in autopsies at this hospital during the past decade, from 0.34% of autopsies during the years 1917 through 1946 to 0.72% of autopsies during the years 1947 through 1954.

This increase is noted to have been due to an increase in two types of cirrhosis that frequently are associated and are considered to predispose to liver carcinoma, healed acute yellow atrophy and fatty nutritional cirrhosis, and to an increase in the number of cases of liver carcinoma occurring in adult patients without underlying cirrhosis.

A striking association of liver carcinoma with healed acute yellow atrophy of the liver, 13.1%, was noted in this series. The occurrence of liver carcinoma in hemochromatosis was 7.7%, and in fatty nutritional cirrhosis it was 2.4%.

Although a definite clinical syndrome is lacking, certain clinical and laboratory features are set forth in this study that may lead to a clinical diagnosis of liver carcinoma.

The frequency with which esophageal varices, peptic ulcers, and intraperitoneal hemorrhage occurred in patients with liver carcinoma, 43.4%, is noted. Twenty-five per cent of the patients with liver carcinoma died as the result of hemorrhage from one of these three sites.

The present conservative therapy of liver carcinoma offers a patient only a limited and hopeless prognosis. Nevertheless, there is no evidence to show that any specific form of therapy may be advocated at the present time.

Dr. G. Kenneth Mallory gave encouragement and assistance during the course of this study.

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Case Reports

Hemorrhagic Diathesis Due to Factor VII Deficiency

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Coagulation disturbances in the second stage of clotting are basically due to deficient generation of thrombin. The prolonged one-stage prothrombin time readily places the defect in the second stage of clotting. Prior to the identification of the plasma and serum prothrombin conversion accelerators, such cases were labeled hypoprothrombinemias.[1-9, 29]

With the identification of Factor V, cases of prolonged one-stage prothrombin time due to deficiency of this substance were separated from the hypoprothrombinemias. The accelerating effect of normal serum on bishydroxycoumarin (Dicumarol) plasma was noted,[10, 11] and de Vries et al.[12] found that if normal plasma was diluted 1:20 with adsorbed plasma the prothrombin time of the mixture was considerably shortened by 1/20 volume of normal serum. They showed that the effect was not due to Factor V and that the effect was abolished by using adsorbed serum. They called the factor SPCA-serum prothrombin conversion accelerator.

Owren[13-15] proposed the name convertin for the serum accelerator of prothrombin conversion and postulated an inactive plasma precursor, proconvertin. Koller et al.[16] identified a serum accelerator of prothrombin conversion which they called Factor VII.

It is now generally agreed[17] that SPCA, convertin, and Factor VII, as well as co-thromboplastin[18] and stable factor, are the same.

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With the advent of techniques for identifying the various factors concerned in the conversion of prothrombin, cases of "hypoprothrombinemia" have diminished until instances of pure hypoprothrombinemia, of a congenital type, exist rarely, if at all. The decrease in such cases has seen a concomitant increase in reports of Factor VII deficiency. There is now little doubt that many of the earlier cases of hypoprothrombinemia were actually Factor VII deficiency[7-9]. Indeed, Frick and Hagen[19] restudied their earlier case and relabeled it as such.

The first case of bleeding due to deficiency of this factor was described by Alexander et al., in 1951.[20] This same group, a year earlier, had reported a case of hypoprothrombinemia which, in retrospect, was probably also a Factor VII deficiency.

Following the original report other cases appeared,[15, 19, 21-23] and Alexander[17] refers to six additional cases of which he has knowledge. The latter group presumably includes Quick's[24] reevaluated case. The recent case of Newcomb et al.[25] should probably be included, although in this instance prothrombin was also deficient.

Thus, some 15 cases of Factor VII deficiency have been described, and at least 3 of the earlier cases of hypoprothrombinemia are, no doubt, additional examples.

Report of Case

A 32-year-old Negro man, a machine operator, was first seen in November, 1955, for study of a hemorrhagic diathesis.

Previous History.—He first recalls being troubled with bleeding at the time of childhood vaccination. Bleeding from minor cuts was troublesome as a child. At the age of 7 or 8 he had a tooth

extracted and was hospitalized. About 15 years ago he experienced bouts of stiffness and swelling of the elbows, shoulders, and hips, usually in the winter months, accompanied by frequent sore throats. This ceased 10 years ago without treatment, and there has been no further joint disturbance, nor is motion limited.

In 1952 he was hospitalized for excessive bleeding following a tooth extraction and received two transfusions. In January, 1955, he developed an infected, traumatic, hematoma which subsided with incision, compresses, and antibiotics. In May, 1955, he lacerated the right forearm and was again hospitalized because of bleeding. He was treated with antibiotics, vitamin K, and 500 ml. of fresh blood. He has had no excessive bleeding since. General health is otherwise excellent.

Family History.—Two brothers and three sisters are living and well, with no bleeding tendencies. One sister died in 1931 at the age of 13 of vaginal bleeding. This sister was said to have had excessive menses from the onset of the menarche. The subject of the report has three children, none of whom has shown any bleeding diathesis.

Physical examination shows a Negro man with massive muscular development. The sclerae are clear. Heart and lungs are normal. Liver and spleen are not palpable. There is no lymphadenopathy.

Methods of Study

1. Hemoglobin, white cell count, and peripheral smear examination by the usual methods.
2. Bleeding time (Duke), coagulation time (Lee-White) and 24-hour clot retraction.
3. One-stage (Quick) prothrombin time.[28]
4. Plasma prothrombin assay: by a modified Owren's procedure,[15] with simultaneous determinations on normal and bishydroxycoumarin plasmas.
5. Prothrombin consumption test.[27]
6. "Corrected" prothrombin consumption test; 0.05 ml. of old normal serum is added to 0.1 ml. of the patient's citrated (one hour old) serum and the prothrombin time of the mixture determined. Simultaneous determination is done on citrated normal (one hour old) serum. Fresh adsorbed plasma is used as the substrate.
7. Serum prothrombin assay. Fresh adsorbed plasma and old normal serum are mixed with dilutions of old patient's serum and prothrombin times determined. Separate prothrombin times are done on each sera with the adsorbed plasma.
8. Variations in recalcified plasma clotting time and variations in the one-stage (Quick) prothrombin time.[28]
9. Factor VII assay.
   (*a*) By the method of de Vries et al.[12]
   (*b*) Bishydroxycoumarin plasma is diluted with equal parts of fresh adsorbed plasma. Aliquots are mixed with various dilutions of the patient's old serum and the prothrombin times determined. Simultaneous assays are done on old normal and old bishydroxycoumarin sera.

Results

1. Hemoglobin, white cell count, platelet count, and differential white cell count were well within normal limits.
2. Bleeding time varied from 3½ minutes up to 30 minutes. Coagulation time varied from 22 minutes up to 30 minutes. Clot retraction was complete.
3. One-stage prothrombin time varied from 150 to 270 seconds (control, 14 seconds).
4. Plasma prothrombin was high normal (Figure).
5. Prothrombin consumption test.
   Patient's serum—infinite time (no clot).
   Normal serum—31 seconds.
6. Corrected prothrombin consumption test (0.05 ml. old normal serum added).
   Patient's serum—11 seconds.
   Normal serum—35 seconds.
7. Serum prothrombin assay. After two weeks of storage the patient's serum still showed prothrombin levels approximating normal plasma (Figure).
8. Variations in recalcified plasma clotting time and prothrombin time of mixtures (Tables 1 and 2). Normal plasma, normal serum, and aged plasma corrected the patient's defect.

TABLE 1.—*Variations in Recalcified Plasma Clotting Time* *

Added Reagent	Clotting Time of Mixture
None	17 min.
Normal plasma	3 min. 10 sec.
Bishydroxycoumarin	5 min. 20 sec.
Adsorbed plasma	9 min.
Normal serum	2 min.
Aged plasma	4 min.

* Nine volumes of patient's plasma is added to one volume of the various plasmas and serum; 0.2 ml. of mixture is recalcified with 0.2 ml. 0.02 M $CaCl_2$.

TABLE 2.—*Variations in One-Stage Prothrombin Time**

Substrate, 9 Vol.	Added Reagent, 1 Vol.	Prothrombin Time of Mixture, Sec.
Patient's plasma	Normal plasma	23
Patient's plasma		270
Patient's plasma	Dicoumarol plasma	55
Patient's plasma	Adsorbed plasma	330
Patient's plasma	Normal serum	18
Patient's plasma	Aged plasma	25
Patient's plasma	Patient's serum	235
Aged plasma		70
Aged plasma	Patient's plasma	27
Bishydroxycoumarin plasma		38
Bishydroxycoumarin plasma	Patient's plasma	38
Adsorbed plasma	Patient's plasma	330
Normal plasma	Patient's plasma	16

* Nine volumes of substrate added to one volume of various sera and plasma.

TABLE 3.—*Factor VII Assay by Method of de Vries et al.*

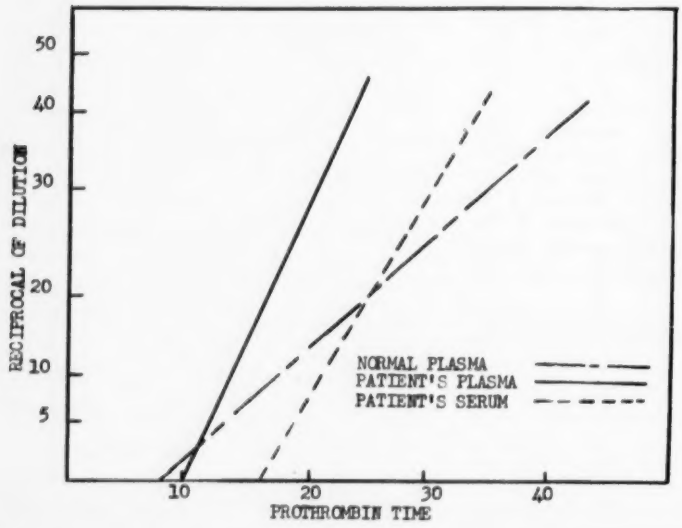
Mixture	Prothrombin Time of Mixture, Sec.
Normal plasma 0.05 Ml. Adsorbed plasma 0.9 Ml. Saline 0.05 Ml.	35
Normal plasma 0.05 Ml. Adsorbed plasma 0.9 Ml. Oxalated normal serum 0.05 Ml.	27
Normal plasma 0.05 Ml. Adsorbed plasma 0.9 Ml. Oxalated patient's serum 0.05 Ml.	38
Patient's plasma 0.05 Ml. Adsorbed plasma 0.9 Ml. Oxalated normal serum 0.05 Ml.	30
Patient's plasma 0.05 Ml. Adsorbed plasma 0.9 Ml. Saline 0.05 Ml.	No clot

Adsorbed plasma and bishydroxycoumarin plasma had no, or reduced, effect. The patient's plasma did not inhibit normal plasma, corrected aged plasma, but had no, or reduced, effect on adsorbed plasma and bishydroxycoumarin plasma.

9. Factor VII assay.
   (*a*) Both patient's plasma and serum showed an all but complete deficiency by the method of de Vries et al. (Table 3).
   (*b*) Assay against dilute bishydroxycoumarin plasma showed near zero values (Table 4).

TABLE 4.—*Assay for Factor VII, Using Fifty per Cent Bishydroxycoumarin Plasma*

Dilutions	Prothrombin Time with Substance Added: Normal Serum	Bishydroxycoumarinized Serum	Patient's Serum	Saline
Undiluted	15	26	26	25
1:5	14	22	24	--
1:10	17	22	21	--
1:20	19	23	21	--
1:40	24	--	24	--



Plasma prothrombin assay. Prothrombin time in seconds plotted against logarithm of reciprocal of plasma or serum dilution.

Comment

Factor VII has been well characterized in recent reviews.[15, 17] It occurs as an inactive precursor in the plasma as proconvertin. Owren states that proconvertin does not act directly on prothrombin but that it first interacts with thromboplastin, in the presence of calcium, to produce the active prothrombin-convertin principle, convertin. Without prior formation of convertin no thrombin will be elaborated under physiological conditions. Reduction in the quantity of the factor delays the formation of thrombin, resulting in a prolonged one-stage prothrombin time. This active principle can be induced by addition of tissue thromboplastin and calcium to whole plasma, serum, or—in isolated systems—to partially purified conversion accelerator.[17]

This factor is relatively stable on storage, and serum is rich in both proconvertin and convertin. It can be adsorbed by Seitz filter and the usual prothrombin adsorbents. Owren has found that ox plasma proconvertin is adsorbed by a 20% asbestos filter while the filtrate contains only prothrombin. During aging of the plasma the active form, convertin, gradually evolves.

Deficiency of this factor results in a hemorrhagic diathesis. The one-stage prothrombin time is prolonged. Bleeding and coagulation times are variable. Most cases have shown normal levels of prothrombin and Factor V, a marked deficiency of Factor VII, and are corrected by normal serum and old or fresh plasma. Response to vitamin K is usually poor. Some cases have shown a familial tendency. In contrast to the rare congenital types, acquired Factor VII deficiency is relatively common occurring as a result of hepatic disease, in the neonatal period, and routinely during bishydroxycoumarin therapy.

The present case shows the characteristics of a Factor VII deficiency. The one-stage prothrombin time is prolonged, as are bleeding and coagulation times. The defect is corrected by normal plasma, Factor-V-deficient plasma, and old serum. Adsorbed plasma has no effect, and bishydroxycoumarin plasma is only partly effective. The patient's plasma does not inhibit normal plasma, corrects Factor-V-deficient plasma, and has no effect on bishydroxycoumarin plasma, or adsorbed plasma. In stored serum prothrombin is present in high titer and Factor VII in extremely low titer. There is no direct evidence of a familial disease, although the family history suggests the possibility in one sister. Prothrombin and clotting times were normal in a sister and brother. Vitamin K therapy was without effect.

An unusual finding in this case is the very low prothrombin consumption. This is quite at variance with Alexander's and Owren's cases, in both of which prothrombin had virtually vanished 60 minutes after the blood was shed. In the present case serum prothrombin levels remained high for several weeks. Since the prothrombin time is quite prolonged, the difference in prothrombin consumption may merely be a difference in the degree of the deficiency. Quick, however, states that consumption is normal in Factor VII deficiency.[24]

The final proof of any clotting defect lies in the failure of the suspected blood to correct or be corrected by blood with a known similar defect—something few laboratories are in a position to determine.

Summary

A patient with Factor VII deficiency is herewith reported. The patient had a lifelong bleeding tendency. Proof of a familial disease was lacking, although suggestive in a deceased sibling. The one-stage prothrombin time was markedly prolonged, and bleeding and coagulation times, moderately so. The defect was corrected by Factor-V-deficient plasma, fresh plasma, and stored serum. Adsorbed and bishydroxycoumarin plasmas were without effect. Plasma prothrombin level was normal. Factor VII was all but absent in the plasma and stored serum. An unusual feature was the very low prothrombin consumption. Serum prothrombin levels remained high for weeks. Vitamin K therapy was without effect.

Mary Washington Hospital.

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Isolated Pulmonary Cryptococcosis

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While it is still a rare disease, over 200 cases of human cryptococcosis have been reported in the literature. The vast majority of these cases show involvement of the central nervous system. The lungs are believed to be the next most frequently diseased site. In fact, the respiratory tract is considered by many [5,6,8] to be the portal of entry of Cryptococcus neoformans. In spite of this, the literature available to us contained reports of fewer than 25 cases of pulmonary cryptococcosis without associated central nervous system or other involvement.

Berk and Gerstl [4] reviewed the literature in 1952 and found five cases of primary pulmonary cryptococcosis; they also reported one case of their own treated by lobectomy. Baker [1] reported three cases of primary pulmonary involvement which were successfully resected. Linden and Steffen [7] reported an interesting case of cryptococcal pneumonitis that developed in a patient receiving corticotropin and cortisone for pemphigus vulgaris. The cryptococcosis apparently was limited to the right lung and underwent a slow spontaneous resolution in a six-week period. In a report of 15 cases dealing with the pulmonary lesions in cryptococcosis, Haugen and Baker [6] described three cases of the disease confined to the lungs. These three patients were surgically treated, with apparent cure obtained in each case. One case of pulmonary cryptococcosis with surgical removal of the lesion followed by potassium iodide therapy was reported by Nichols and Martin.[8] Eight cases of cryptococcosis confined to the lung were included in a report by Baker and Haugen [2] dealing with tissue changes observed in tissue specimens of twenty-six cases of cryptococcosis submitted to them for pathology review.

Haugen and Baker [6] stress the importance of prompt therapy of pulmonary cryptococcosis, pointing out that cryptococcus organisms may disseminate from lesions in the lung and eventually produce death, while the initial pulmonary lesion may heal so completely as to show no evidence whatsoever of previous involvement.

In all but one of the successfully treated cases, surgical removal of the diseased lung tissue was performed. Taber,[9] Berk and Gerstl,[4] and Baker [1] were all of the opinion that early and complete resection of the involved lung tissue offered the patient the best treatment and optimum assurance against further dissemination of the organisms.

In keeping with and strengthening this concept we are reporting a case of cryptococcosis confined to the lung and treated surgically with apparent success.

Report of Case

The patient was a 15-year-old high school boy who was first seen on Jan. 6, 1955. He had been well until six weeks prior to this date. At that time he noted that he was becoming easily fatigued and somewhat weak and developed a dry hacking cough with a mild pleuritic pain on the left. During the entire illness he had lost about 10 lb in weight. He said that he felt cold all the time but did not have any chills or night sweats. His parents had taken his oral temperature several times but had always found it normal. A microfilm showed a suspicious lesion in the left lung, and he was referred to the Lexington Clinic for further study.

On physical examination he appeared chronically ill, he had a dry hacking cough, his pulse was 84, his temperature was 99.4 F, and physical

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From the Lexington Clinic and the Central Baptist Hospital.

examination of the chest showed no abnormalities. The red blood cell count and hemoglobin were normal. The white cell count was 11,000, with 78% polymorphonuclear leukocytes, 16% lymphocytes, 5% monocytes, and 1% eosinophiles. The Westergren sedimentation rate was 5 mm. per hour, the Kahn was negative, and the urine was normal.

X-rays of the paranasal sinuses showed cloudiness in the left ethmoid, the left frontal, and both maxillary sinuses. A 6 ft. film revealed infiltration of the left lower lobe of the lung, with two cavities (Fig. 1).

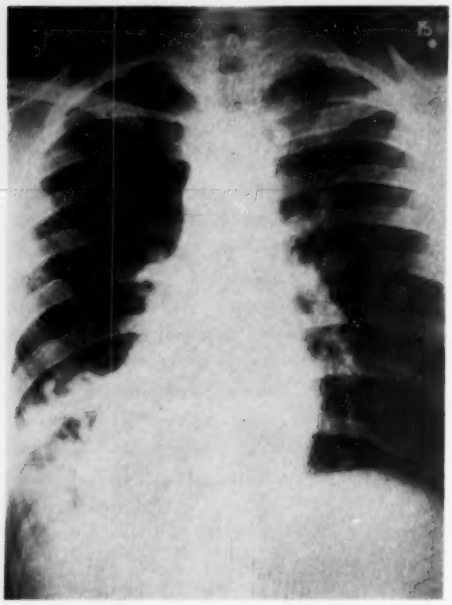

Fig. 1.—Chest x-ray, showing infiltration of the left lower lobe of the lung.

He was then admitted to the hospital for diagnosis and treatment. No sputum was obtainable. Bronchoscopy showed no abnormalities, and bronchial washings were negative for significant pathogens, including acid-fast bacilli and fungi. Histoplasmin skin test showed a 3+ reaction; P. P. D. first strength, Blastomyces, coccidioidin, and torulin were all negative. Bronchograms indicated that the cavities previously seen on a chest film did not communicate with the bronchial tree.

On Jan. 17, 1955, a thoracotomy was performed. The patient was placed on his right side under general positive pressure anesthesia. A left posterior lateral incision was made. The fifth rib was sectioned posteriorly, and the chest was entered through the fourth interspace. The entire left lower lobe was involved in the pathological process. It was hard and rubbery, and all segments were involved. The upper lobe of the left lung was free of any gross evidence of disease. There were no remarkably enlarged lymph nodes in the hilum. The mediastinal structures appeared to be normal. A left lower lobectomy was carried out without difficulty, beginning the dissection in the major fissure and with individual ligation of the hilar structures. An open closure of the bronchus was done and a pleural flap applied. Following the removal of the lobe, one or two nodes in the hilus, which had been exposed during the dissection, were removed. The pleural cavity was lavaged and the chest closed in layers with interrupted nonabsorbable surgical (silk) sutures. Water-seal bottles were placed in the second anterior interspace and posterior lateral seventh interspace. The patient received 1000 cc. of blood during the operative procedure. The postoperative course was not complicated. The lung expanded readily. The anterior tube was removed on the first postoperative day and the posterior tube on the second. The patient received chest exercises, both pre- and postoperatively, so that his lung function and chest wall function were excellent within a week after the operation. The wound healed per primam, and the sutures were removed on the sixth postoperative day.

The surgical specimen consisted of the entire lower lobe of the left lung, which weighed 320 gm. and generally retained the normal tetrahedral shape of the lobe, measuring 12 cm. on a side. The superior segment of the lobe was essentially normal. The other segments (lateral basal, posterior basal, and anteromedial basal) were nearly completely consolidated. The cut surface showed the appearance of confluent granulomatous lesions with multiple areas of necrosis and abscess formation. The necrosis was dry and friable rather than caseous or mucoid.

The fresh cut surface had a mottled yellowish-gray-tan color. The microscopic tissue changes have been grouped according to the plan set forth by Baker and Haugen.[2] There were virtually no polymorphonuclear leukocytes in the typical parts of the lesion. In the areas where there was necrosis there was a moderate infiltration of polymorphonuclear leukocytes. Lymphocytes were present, and plasma cells were present in large numbers. Macrophages were present in large numbers, often containing yeast-like organisms. The reaction of giant cells was intense (4+), and intracellular organisms were usually present. The most conspicuous feature of the lesion was the large number of multinucleated foreign-body giant cells (Fig. 2). There was considerable necrosis with microscopic and larger abscesses. There was a

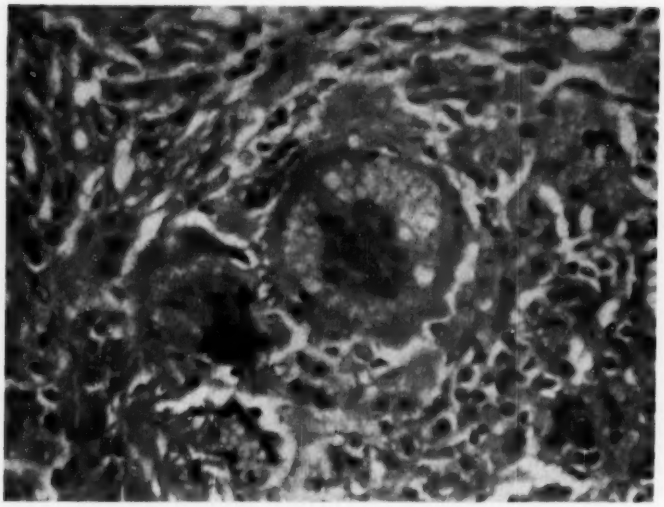

Fig. 2. — Photomicrograph of a section of the involved lung, showing multinucleated giant cells with numerous yeast-like organisms.

very heavy degree of fibrosis. Calcification was not observed.

Since the saprophytic existence of C. neoformans is well established, it was felt that mouse inoculations should be carried out to confirm identification and to establish pathogenicity by fulfilling Koch's postulates. Accordingly, a series of four white mice were inoculated with a heavy saline suspension made from the original culture isolated from the lower lobe of the left lung. Two mice received 0.1 ml. of the suspension intracerebrally, and the other two received 0.5 ml. and 1.0 ml. intraperitoneally, respectively. In two weeks the mice receiving the intracerebral inoculations showed a markedly staggering gait, and their coats were rough. On autopsy, both of these mice showed marked involvement of the brain, and there were white lesions scattered throughout the lungs. The spleen of each mouse was enlarged but showed no other signs of gross pathology. Microscopically the lungs showed extensive granulomatous lesions similar to those seen in the patient (Fig. 3). India-ink preparations were made from the exudate around the brain, which showed marked capsule formation (Figs. 4 and 5).

Four weeks after inoculation the mice that had received the intraperitoneal inoculations were killed and autopsied. These mice showed an increased amount of abdominal fluid. The mesentery of both mice was white and thickened with enlarged lymph

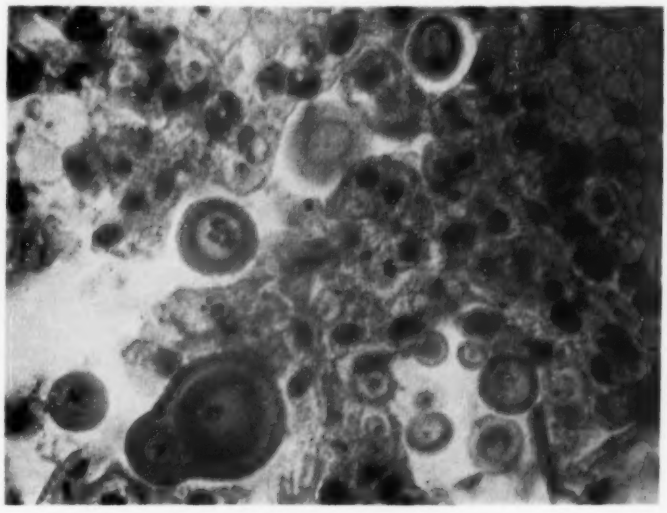

Fig. 3. — Photomicrograph of a section of mouse lung inoculated with the isolated organism, showing numerous encapsulated yeast-like cells and extensive inflammatory lesion.

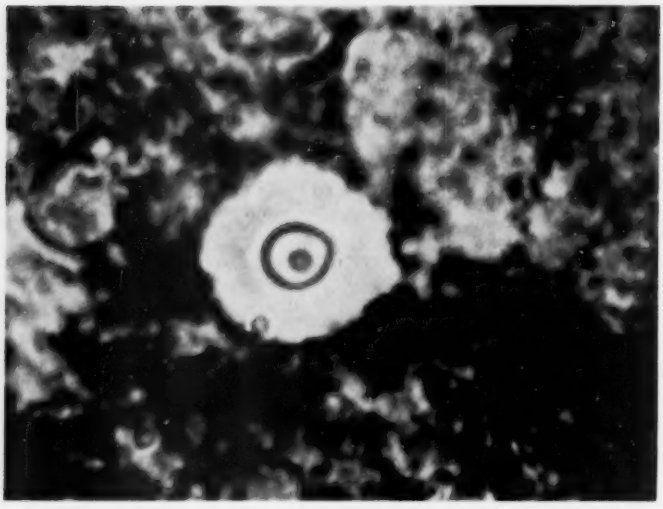

Fig. 4. — Photomicrograph of an India-ink preparation from the exudate around mouse brain, showing a typical encapsulated Cryptococcus neoformans cell.

nodes. There were large fibrotic, granulomatous lesions on the surface of the livers, suggestive of those seen in the lung of the patient. In the spleen of one of these mice there was a large cystic space. The brain of both mice showed many cystic spaces (Fig. 6). All of the above-mentioned tissues were examined microscopically and showed numerous encapsulated budding yeast-like organisms as well as extensive granulomatous inflammatory reaction.

Cultures from the various involved organs of all four mice were made in duplicate on blood agar and Sabouraud's medium. In each instance a luxuriant growth of yeast-like organisms was obtained with an equal amount of growth at 37 and 22 C. At no time was there any evidence of mycelial formation at either temperature. The organisms continued to produce capsules, though not as prominent on subsequent subculture. With age the cultures took a dull yellow pigmentation and became quite mucoid in consistency. Capsular swelling tests were performed by Dr. Margaret Hotchkiss, of the University of Kentucky, who felt that demonstrable capsular swelling did occur. In general the cultures conformed with the criteria set forth by Benham.[8] It is our opinion that this culture is a variety of C. neoformans and that Koch's postulates have been adequately fulfilled to demonstrate the pathogenicity of the organism.

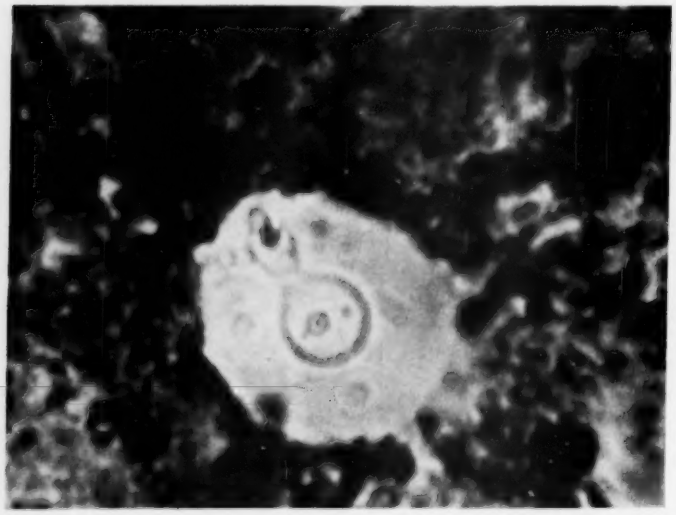

Fig. 5. — Photomicrograph of an India-ink preparation from exudate around mouse brain, showing heavily encapsulated budding yeast-like cell of Cryptococcus neoformans.

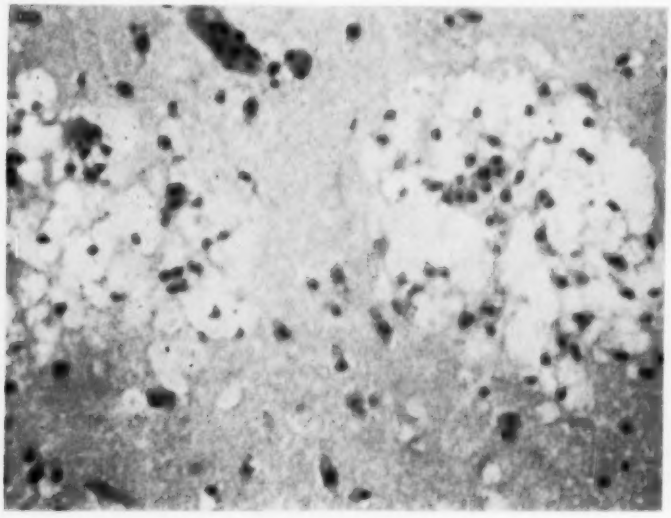

Fig. 6. — Photomicrograph of a section of mouse brain inoculated with Cryptococcus neoformans, showing cystic spaces containing organisms.

Comment

The patient made an uncomplicated recovery and returned to his usual activities, including high school basketball. One year after surgery his chest x-ray was clear, and his health was excellent. This patient showed surprisingly little systemic reaction in view of the widespread destruction of lung tissue, and we believe that the successful clinical result obtained was chiefly due to the early surgical removal of the diseased lung tissue.

Summary

A case of isolated pulmonary cryptococcosis in a 15-year-old boy who was successfully treated by means of lobectomy is presented. The clinical, surgical, and pathological aspects of the disease are discussed. We believe that surigcal resection of the involved lobe affords the best means of effecting a successful cure.

Dr. J. T. McClellan assisted in the preparation of the pathological material in this paper.

Lexington Clinic, 190 N. Upper St. (15).

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Indeterminate Leprosy Acquired During Military Service

Report of a Case and Review

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A recent case of leprosy posing a diagnostic problem was seen by us at Fort Bragg, N. C. This disease is so unusual in the army that we feel this case worth publishing. In addition, a review of military experience with leprosy is presented, with recent concepts in diagnosis and therapy.

Report of Case

A 59-year-old white man, an officer, was admitted to U. S. Army Hospital, Fort Bragg, N. C., from the Orthopedic Clinic on April 1, 1954, for observation of skin lesions of the left lower leg, suspected to be due to Hansen's disease. The patient stated that he first noted a slightly red area on the lateral aspect of the left ankle in July, 1951. He consulted a physician after the lesion had been present for about one month, when it was about the size of a quarter. He was given nonspecific therapy after a diagnosis of contact dermatitis was made.

The lesion gradually enlarged. Approximately six months before admission, another, similar area developed proximal to the original lesion. In the six months prior to admission, both lesions, particularly the proximal one, enlarged rapidly, and the patient noted numbness to the touch over the area. In March, 1954, a subcutaneous nodule was noted posterior to the lateral malleolus.

The patient was admitted to the hospital for further study. Past history revealed that he had been a school teacher and superintendent prior to extended active duty in 1941. Prior to service he had never been away from his home in Kentucky and eastern Tennessee. He served in the ETO in 1944-1945 and spent 16 months in the Philippines in 1946-1947. His work at the latter station was primarily of office type. The opportunities for contact are not known precisely. His family was not present with him during this tour of duty.

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The remainder of the history was essentially noncontributory to the present illness. General physical examination revealed no abnormalities; findings were limited to those associated with the present illness.

On the lateral aspect of the left lower leg there were two lesions. The smaller, distal lesion measured approximately 10 cm. in diameter; the proximal lesion was somewhat larger, with an intervening strip of normal skin. The lesions had irregular, sharply defined borders and were irregularly erythematous. The areas were slightly elevated above the normal skin and gave the impression of a diffuse infiltration. There was complete anesthesia to touch, pain, and temperature, which was confined to the lesion. Careful neurological examination revealed no other abnormalities except absence of the left Achilles tendon reflex. There were no palpable superficial nerve trunks.

Sedimentation rate was 18 mm. in one hour, and the serology was negative. The remainder of the laboratory work was within normal limits.

A biopsy was felt to be indicated, as the possibility of leprosy was entertained. At surgery an elliptical section of skin and underlying prominent granulomatous lesion were excised.

Routine sections were strongly suggestive of leprosy, and special tissue stain revealed several acid-fast organisms.

The histamine test was equivocal, since the redness of the lesions made it impossible to see where the flare was. The methacholine (Mecholyl) test demonstrated absence of sweating in the areas of pathology.

A punch biopsy was done. Section of this by our pathologist and by the Armed Forces Institute of Pathology confirmed the diagnosis of leprosy. Several acid-fast organisms were demonstrated in these sections.

The patient was retired from Service and transferred to the U. S. Public Health Service Hospital, Carville, La.

Lepromin test at Carville was reported as negative, and it was felt by the attending staff that this represented a case of leprosy of the indeterminate group.

Fig. 1.—Low-power magnification. Early granulomatous infiltrate of dermis, particularly in the upper zone and surrounding the blood vessels and nerves. Caseation necrosis is absent.

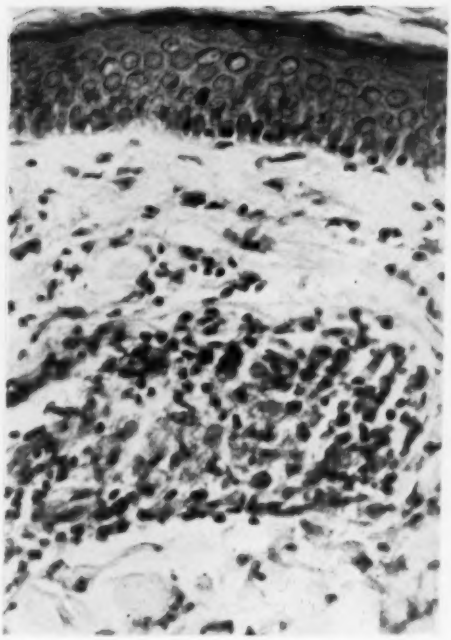


Fig. 2.—Medium-power magnification. The infiltration consists of early epitheloid cell tubercles associated with an admixture of lymphocytes, particularly at the margins.

Comment

Leprosy has always been of considerable concern to the armed services. An excellent article on this subject by Aycock and Gordon,[1] in 1947, summarizes the experiences of the services with leprosy up to that time. The first case of leprosy among United States Army personnel was reported in January, 1903. In the period from 1903 to 1921, twenty-seven cases of leprosy were reported in members of the United States Army. Of these, 21 were natives of the Philippines and Puerto Rico and were therefore brought up in endemic areas. The remaining six were soldiers from the continental United States.

From 1921 to 1940, thirty-two Spanish-American War veterans were admitted to the U. S. Marine Hospital suffering from leprosy. Thirty patients had military service outside the United States in places known as foci of leprosy, such as Puerto Rico, Cuba, Hawaii, China, and the Philippines, twenty-five had service in the Philippines. During the same period, 51 World War I veterans were admitted also. The records of 33 show no service outside the United States, and only 6 had a record of service in foreign countries which are foci of the disease.

At any rate, the above statistics do indicate that service men returning from areas of endemic leprosy should be watched closely for evidence of the disease. A recent case was reported by Dr. Norman E. Levan.[2] This case occurred in a native-born Kansan who served in the Philippines from September, 1944, to September, 1945. He developed a painless ulceration on the left calf in July, 1945, which healed, leaving an anesthetic scar. The scar gradually enlarged over the next seven years, and in December, 1952, he incurred a painless burn at the site of the original ulcer. The diagnosis of

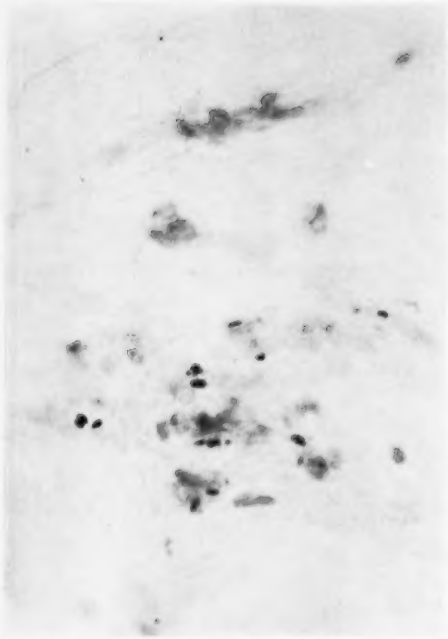


Fig. 3.—High-power magnification (oil immersion), Ziehl-Neelsen Stain. In the center, bundles of lepra bacilli, Mycobacterium leprae, are present.

leprosy was entertained but apparently not proved until June, 1953, when a number of faint, pink, hypesthetic macules with slightly thickened edges appeared on the patient's chest, back, upper arms, and thighs and were investigated. Lepromin test was negative, and it was felt that this case belonged to the indeterminate group. The case is under treatment with sulfoxone (Diasone) on an outpatient basis while he continues his work as a garage mechanic. He is complying with necessary regulations for modified isolation.

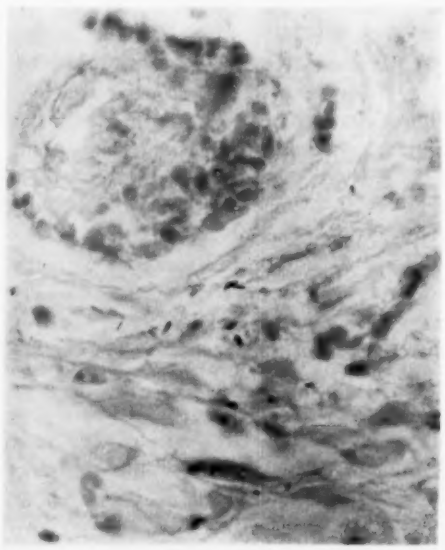
Statistics on Disability Separations Due to Leprosy

Year	Service Connected	Non-Service-Connected	Total
1942	0	9	9
1943	1	6	7
1944	3	2	5
1945	5	1	6
1946	0	1	1
1947	10	3	13
1948	8	0	8
1949	3	1	4
1950	3	0	3
1951	2	1	3
1952	1	3	4
1953	3	1	4

The epidemiology of leprosy is not clear. It would appear that "inherited susceptibility" (Aycock) is a most important concept. The apparent immunity displayed by some who have had almost constant contact is baffling. Two most interesting cases are the two marines from Michigan, tattooed by the same man on the same day in Melbourne, Australia.[3] Approximately two and one-half years later they both developed tuberculoid leprosy in these tattoos. These cases have been commented on by Dr. John Lowe, of the Nigeria Leprosy Service, who has seen cases of leprosy that he feels were caused by inoculation with nonsterile tattooing needles.[4]

The recent book of Arnold[5] was relied upon heavily as a guide in our case and is recommended for the libraries of all installations seeing veterans. It would appear that familiarization with the subject of leprosy is of paramount importance in making a diagnosis. Recent advances in therapy with the sulfone group of drugs have radically changed the prognosis in this disease.[6]

Fig. 4.—High-power magnification (oil immersion), Ziehl-Neelsen Stain. Numerous lepra bacilli are present about the blood vessels and nerves. Several bundles of bacilli are lying in "chopstick" fashion.



There are two main types of leprosy. Lepromatous leprosy is the progressive and malignant form. The defense of the body is virtually lacking in this type, and a generalized systemic infection tends to occur. The lepromin test (Mitsuda reaction) is negative. Tuberculoid leprosy is the relatively benign (except for nerve destruction), generally self-limited form. The lepromin test is positive, which seems to denote that the body has some defense against the infection. The "indeterminate group" comprises those cases, generally with pale macules clinically, that are not readily classifiable as lepromatous or tuberculoid in type.

In general, it can be said that leprosy is a disease of the skin and nerves. If confronted with the task of proving or disproving the diagnosis in a given patient, one should carefully consider the three possible categories. For instance, the lepra bacilli are difficult to find in the tuberculoid type but are always numerous in the skin biopsy of an active lepromatous case.

As pointed out in Arnold's book, the early case of leprosy may exhibit a bizarre appearance. Suspicion should be aroused by "spots and blotches," "lumps and nodules," and skin disease with neuritis.

It has been remarked erroneously that the fingers and toes "drop off." Actually the "loss" is due to neurotrophic bone absorption with resultant shortening of the digit.[7]

Summary

A case of leprosy in an Army officer stationed in the Philippines in 1946 and 1947 is presented. It has been predicted by leprologists that an increasing number of cases will be seen in our veterans of World War II. Suspicion should be high among military and civilian physicians alike, particularly with our continued troop concentrations in the far East. A few of the salient features of leprosy with recent advances are presented.

Dr. Harry Arnold Jr., of Honolulu, T. H., reviewed this manuscript and made editorial comments, and Capt. Joseph Teresi described the pathological material.

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Chronic Idiopathic Jaundice with Unidentified Pigment in Liver Cells

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In 1954 Dubin and Johnson[1] reported 12 cases of idiopathic jaundice with an unidentified pigment in the centrilobular liver cells. Clinically, these patients could have been classified as cases of "familial hyperbilirubinemia" or chronic hepatitis. However, with the unusual liver biopsy finding of a previously undescribed pigment, a new clinical entity was suggested. Since the original description, four additional cases have been recorded.[2-5] It is our purpose to record an additional case of this entity.

Clinically, in addition to mild recurring icterus of unexplainable cause, these cases are characterized by (1) vague abdominal discomfort, (2) dark urine which is positive for bilirubin, (3) hepatomegaly, (4) poor visualization of the gall bladder by oral dye methods, (5) one-minute bilirubin values which are elevated to at least 50% of the total bilirubin and an otherwise benign course with a good prognosis for life.

The diagnosis of these cases can only be proved by liver biopsy. Grossly, the specimen is a blue-black color. Histologically, the liver appears normal except for the presence of the pathognomonic coarse brown granules in the liver cells in the central vein areas.

Report of Case

A 31-year-old housewife of Italian extraction was admitted to Montgomery Hospital on Jan. 8, 1956, with the chief complaints of vague upper abdominal pain and mild jaundice. She recalled that she was first jaundiced at the age of 4 or 5 years and that she had had recurrent attacks of jaundice many times since then. None of her early episodes of jaundice were serious enough to require hospitalization. They were not associated with chills or fever. Four weeks prior to admission, she noted onset of jaundice associated with weakness and generalized upper abdominal pain of a vague nature. The pain seemed to radiate from the epigastrium bilaterally across the abdomen and sometimes to the back. It occurred usually after eating and at times during a meal. Three cholecystograms performed prior to admission were reported as "nonfunctioning gall bladder."

Past History.—In September, 1946, she was admitted to another hospital with "gall bladder symptoms." She manifested mild jaundice and upper abdominal distress. X-ray studies revealed nonfunctioning gall bladder. Studies then showed serum bilirubin, 3 mg. per 100 cc.; urine, negative for bile; normal red cell fragility test; normal biliary drainage.

In October, 1946, she had additional studies performed at still another hospital. X-ray findings showed normal barium enema and poor concentration of dye in gall bladder. Laboratory findings were total serum bilirubin, 3.1, 1.9 mg.; cholesterol, 314 mg. per 100 cc.; total protein, 7 gm. per 100 cc.; A/G ratio, 5.2/1.8; prothrombin time, 100%; cephalin flocculation, +4; B. S. P., 5% retention.

Systemic Review.—Her appetite had been fair. She had witnessed no nausea or vomiting. Her urine had been the color of strong tea. There had been a 10 lb. weight loss during the past year. She did not smoke or drink.

Family History.—She was married and had two healthy children, 3 and 4 years of age. Her father was living and well. Mother had died of "heart attack." Three brothers and one sister were living and well. There was no family history of jaundice or blood dyscrasia.

Physical examination revealed a well-developed woman with mild generalized jaundice. Head, neck, heart, and lungs were normal. Abdomen was soft. The liver edge was not palpable, but slight tenderness was noted in the right upper quadrant of the abdomen. The spleen was not palpable. Blood pressure was 120/80, and temperature, pulse, and respiration were normal.

Submitted for publication July 11, 1956.

From the Departments of Pathology and Medicine, Montgomery Hospital.

Laboratory Findings (Jan. 1-25, 1956).—Urinalysis: bile, positive; urobilinogen, positive 1:10. Hemogram: Hgb., 11.5 gm.; RBC, 3,870,000; WBC, 6900; polymorphonuclear leukocytes, 57; lymphocytes, 41; eosinophiles, 2; reticulocyte count, 0.6%. Total serum bilirubin, 3.65 to 3.9 mg. per 100 cc. Total protein, 5.8 gm. per 100 cc. Cephalin flocculation ± to +3; A/G, 4.07/1.73. Thymol turbidity, 2.5 units. Alkaline phosphatase, 2.4 Bodansky units. Prothrombin time, 94%. Sugar, 97 mg. per 100 cc. Sternal bone marrow smears showed normal findings; Coombs' test was negative; red cell fragility test was normal.

X-Ray Findings.—Normal gastrointestinal series. Gall bladder studies following the intravenous injection of 40 cc. of sodium iodipamide (Cholografin) showed but faint concentration of dye after 90 minutes, with better filling at the 2-hour period. There was no suggestion of gallstones.

Course in Hospital.—Clinically, the diagnosis of chronic hepatitis was entertained, but a surgical exploration was decided upon primarily to obtain an adequate liver biopsy. At operation the gall bladder and biliary tree were found to be normal, and no evidence of extrahepatic obstruction was seen. The liver was moderately enlarged and presented a striking slate-blue color. A small wedge biopsy was removed, and its cut surface appeared black. Upon formalin fixation the liver biopsy turned dark green-black and later to a mottled dark gray color. Histologic examination of the liver revealed a well-preserved lobular pattern with quiescent hepatic cells. A considerable amount of coarse granular greenish-brown pigment was present in the liver cells. This was most marked centrilobularly (Fig. 1). The pigments were not found within the bile canaliculi. Portal triads were normal. Iron stains of the pigments were negative.

According to Dr. Leo Krainer,[9] of the Armed Forces Institute of Pathology, these pigments were PAS (periodic acid Schiff) positive, oil red O negative and showed dull brown fluorescence. According to him these findings were compatible with chronic idiopathic jaundice, with unidentified pigment in liver cells.

The patient's postoperative course was uneventful, and she was discharged on the 20th hospital day. We have seen her twice since her discharge, and she has remained asymptomatic. On March 6, 1956, her serum bilirubin was 3.1 mg. per 100 cc.; cephalin flocculation, +1, and thymol turbidity, 2 units. On March 28, total serum bilirubin was 2.9 mg. per 100 cc., with 1.9 mg. one-minute fraction. Sulfobromophthalein (Bromsulphthalein) retention was 4.5% at 30 minutes, using 5 mg. of dye per kilogram of body weight.

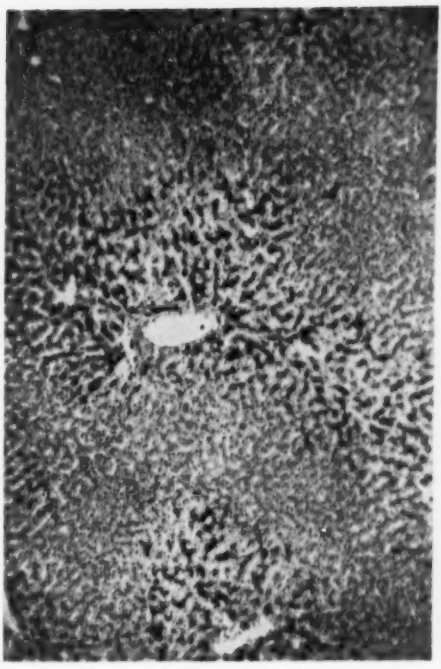

Figure 1

Comment

It is interesting to note that this patient's jaundice began at the age of 4 years. Previously reported cases had not developed until after the 10th year of life. It appears that this disease entity along with the previously described cases of "familial nonhemolytic jaundice" or "constitutional hyperbilirubinemia" must be considered when one confronts cases of chronic unexplained jaundice. Both of these situations if properly recognized not only will categorize the patient diagnostically but also will prevent unnecessary surgery. Furthermore, since as of this writing this disease entity carries with it a good prognosis for life, proper diagnosis alleviates considerable anxiety which the patient naturally has about the jaundice. Our patient had had jaundice since she was 4 years of age and still had not been given a satisfactory explanation concerning her illness. In view of her jaundice, "nonfunctioning" gall bladder, and vague right upper quadrant distress, it is surpris-

ing that she had not been subjected to cholecystectomy.

Clinically, the slight jaundice, the lack of vigor, the upper right quadrant discomfort, and tenderness are characteristic. The liver was found to be enlarged at abdominal exploration but was not felt by physical examination.

It has been stressed previously that the gall bladder is not visualized by oral dye methods. This was the case with our patient. However, the gall bladder was visualized by the intravenous dye method two hours after the dye was given. It is postulated that there is a metabolic defect in the excretion of gall bladder dye by the livers of these patients. However, it seems that if sufficient time is allowed the liver cells will excrete the dye and the gall bladder will be visualized.

The negative Coombs' test, the normal reticulocyte count, and the normal red cell fragility tend to rule out hemolytic factors as a cause for the jaundice.

The liver tests showing slight elevation of bilirubin, mainly one-minute-reacting bilirubin, and slight elevation of the cephalin flocculation have also been characteristic of other reported cases of this entity. The normal sulfobromophthalein excretion is noteworthy, since it has heretofore been reported to be elevated.

Proof of the existence of this disease entity is revealed by gross and microscopic examination of the liver. The slate blue color of the liver was striking and is not seen with the usual variety of liver disorders. Indeed, some have diagnosed this condition by the color of the liver biopsy specimen.

Microscopically, the presence of coarse brownish pigment in the liver cells around the central vein area are pathognomonic (Fig. 2). To date the nature of this pigment is not known. The normal histologic appearance of the liver otherwise excludes the possibility of chronic hepatitis and other chronic liver disease.

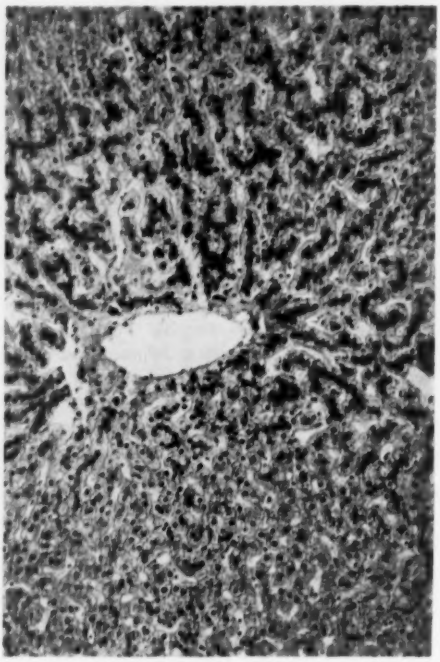

Figure 2

Although the findings on liver biopsy prove the existence of these cases, clinically it is difficult to differentiate this entity from so called chronic hepatitis and cases of "familial nonhemolytic jaundice." In the latter cases, however, the gall bladder usually is visualized, the bilirubin is mainly indirect reacting, the urine is negative for bile, and the liver is normal histologically. It appears that in both "familial nonhemolytic jaundice" and the entity here reported a metabolic defect is present impairing the ability of the liver cells to excrete bilirubin or one of its products. There is no familial tendency in this recently described entity, whereas, a family history of jaundice is frequently obtained in cases of familial nonhemolytic jaundice.

Summary

An additional case of persistent nonhemolytic jaundice with unidentified pigment in the liver is reported. The disease is characterized by persistent jaundice of slight

intensity, malaise, and right upper quadrant distress. It may be mistaken for chronic hepatitis, familial nonhemolytic jaundice, and gall bladder dysfunction. The presence of this entity is proved by the characteristic liver biopsy findings.

Drs. T. J. Natoli and A. J. Fingo permitted us to study this case.

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Neuromuscular Blockade and Artificial Respiration in Severe Tetanus

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Until very recently the treatment of severe tetanus has been an almost hopeless undertaking, the mortality rate ranging upward of 70% for those cases with an incubation period of less than 10 days.[1,2] Once the toxin has become "fixed" to the nerve cell there is no known method of removing it or of counteracting its effects. The disease is, however, a self-limited process which leaves no permanent damage in survivors. The cause of death is usually asphyxia, pneumonia, exhaustion, or cardiac failure.

The main problem in the care of these patients is to produce relaxation of the spastic musculature while maintaining adequate pulmonary ventilation. The severe, and usually fatal, case of tetanus is marked by the very narrow margin between the anoxia produced by spasm of the respiratory musculature and the anoxia secondary to attempts to combat this spasm.

Only in the past few years have there been any reports of the successful treatment of severe tetanus.[3-7] These successes have been achieved by the use of drugs blocking neuromuscular impulse transmission together with artificial respiration. These two therapeutic agents transform the problem of tetanus, with its high mortality rate, into one resembling bulbar poliomyelitis but with the advantage that the degree of paralysis is under the control of the physician.

It is the purpose of this paper to report another example of the successful treatment of severe tetanus with these agents.

More general measures, which are also necessary to the successful care of these patients, have been excellently discussed elsewhere.[8]

Submitted for publication May 28, 1956.

From the Department of Medicine, Stanford University School of Medicine.

Report of Case

A 20-year-old, white, dairy worker crushed his left little finger on a pig trough on Nov. 25, 1955. He immediately consulted a physician, who debrided and sutured the wound and administered 1500 units of tetanus antitoxin and 0.5 cc. of tetanus toxoid. It is not known whether or not the patient had received previous immunization. One gram of dihydrostreptomycin, 100,000 units of potassium penicillin, and 300,000 units of procaine penicillin were given intramuscularly on the day of injury and every other day thereafter.

On Dec. 2, seven days after the injury, the patient awoke with painful back and jaw muscles. He was immediately hospitalized and noted to have very tight neck muscles and trismus. All sutures were removed from the finger, and it was soaked in hydrogen peroxide. The patient was given tetanus antitoxin, 50,000 units intramuscularly and 50,000 units intravenously, on this and the following day.

On Dec. 3 he was opisthotonic. The injured finger was amputated. Meprobamate, 800 mg.; chlorpromazine, 50 mg., and meperidine, 25 mg., were administered every two hours for sedation. Tetracycline and hydrocortisone were also given.

From Dec. 4 to 12 the tetanus gradually became severer. A tracheotomy was performed on Dec. 5. In spite of the use of continuous intravenous alcohol, intravenous thiopental, and depot tubocurare, the patient's respiratory reserve progressively diminished. Tetanic spasms of the thoracic and abdominal musculature became more frequent and severer, and attempts at their control resulted in marked cyanosis.

On Dec. 12 the patient was given a general anesthetic and continuous intravenous succinylcholine and was transferred to Stanford University Hospital.

On arrival he was semicomatose, and respirations were maintained manually by an anesthetist. His color was good. The lung bases were dull to percussion, with decreased breath sounds. The heart was regular at a rate of 84/minute. The heart impulse was strong, and a gallop rhythm was present. The arterial pressure was 170/90 mm.

of Hg. The abdomen was moderately distended and tympanitic. All muscle reflexes were absent; the corneal reflexes were normal. The rectal temperature varied from 37.9 to 40.4 C (100.2 to 104.7 F) during his illness. No other abnormal findings were noted.

The hematocrit was 47 per 100 cc., and there were 12,000 leukocytes per cubic millimeter, with a normal slide differential count. Urine examination was normal. The serum concentrations of sodium, potassium, chloride, carbon dioxide, and urea were normal. An x-ray of the chest revealed atelectasis of the left lower lobe and a mediastinal shift to the left. The heart was normal. A culture of material from the finger stump yielded Escherichia coli and Staphylococcus albus.

On the evening of Dec. 12 the patient was placed in a respirator of the Drinker-Collins type, and a continuous intravenous infusion was begun through an indwelling polyethylene catheter.

The following plan of therapy was adhered to closely:

All medications were given through the tubing of the intravenous set.

The urine output was kept above 1600 cc. by the daily administration of 3000 to 4000 cc. of dextrose and water or saline.

Aqueous penicillin, 300,000 units, was given every four hours.

Injections of 3 to 9 mg. of *d*-tubocurarine were given as needed to control muscle spasms and rigidity.

Secobarbital, 50 to 100 mg.; meperidine, 25 to 50 mg., and later phenobarbital, 60 to 120 mg., were given for agitation and to maintain a base level of sedation.

The patient was turned frequently, the tracheal tube was changed daily, and bronchial aspiration was applied every hour and at other times as necessary.

On Dec. 15 and 16 large amounts of purulent sputum were aspirated at bronchoscopy. On Dec. 15 the spasms reached their height. Tribromoethanol was administered rectally in doses of 4 to 7 gm. on several occasions with excellent results.

The patient then rapidly improved, and on Dec. 17 the *d*-tubocurarine was stopped and the patient was removed from the respirator. His neck was still rigid and hyperextended, but pulmonary ventilation was adequate.

By Dec. 21 the tracheal tube and intravenous catheter had been removed, oral feedings had been resumed, and the chest x-ray revealed clearing of the atelectasis.

The patient's recovery was complete, though he had a total amnesia for the entire period of hospitalization.

Comment

This patient presented the problem typically seen in the severe case of tetanus in which attempts to relax the repiratory muscles result in their paralysis and in depression of the respiratory center. In such formerly fatal cases there is apparently no way to return these muscles to the voluntary control of the patient, and artificial respiration is life-saving. This can be applied by manually controlled bag-breathing or by the mechanical respirator. The latter method is the only one practical for the period of several days that it may be required and has the further advantage of thorough trial in the treatment of poliomyelitis. In either case a tracheotomy is essential to insure an unobstructed airway and to facilitate the application of bronchial aspiration.

Succinylcholine or *d*-tubocurarine is used to produce the necessary muscle relaxation. Woolmer and Cates prefer succinylcholine because they feel that the amount of relaxant required varies from minute to minute, and the effect of *d*-tubocurarine is too prolonged.[3] However, intravenous *d*-tubocurarine was quite effective in the present case, and it seemed advisable to use an agent for which there is a specific antidote (neostigmine [Prostigmin]).

The liberal use of sedation appeared to reduce, but not eliminate, the requirement for relaxants. The ease of use and effec-

Daily Dosage Totals for the Period of Respirator Care

	December				
	13	14	15	16	17
d-Tubocurarine	159 mg.	90 mg.	171 mg.	84 mg.	41 mg.
Secobarbital	1,230 mg.	725 mg.	125 mg.	675 mg.	150 mg.
Meperidine HCl	225 mg.	850 mg.	150 mg.	300 mg.	50 mg.
Phenobarbital	.....	765 mg.	715 mg.	260 mg.	.....
Tribromoethanol	.....	.....	14 gm.	14 gm.	.....
Amobarbital	.....	.....	.....	.....	250 mg.
Pentobarbital	.....	.....	.....	.....	900 mg.

tiveness of rectal tribromoethanol and *d*-tubocurarine in combination were especially impressive.

Summary and Conclusions

A case of severe tetanus with complete recovery following the use of *d*-tubocurarine and a respirator is reported. The prognosis for such patients should be improved and the mortality rates reduced to negligible values by early and intensive use of neuromuscular blockade and artificial respiration.

The many members of the Departments of Medicine, Anesthesiology, and Surgery contributed much time and experience to the care of this patient.

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Hereditary Hemorrhagic Telangiectasia in Three Families

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Hemorrhagic telangiectasia, or Rendu-Weber-Osler's disease, is a hereditary primary vascular entity, characterized by mucosal and visceral telangiectases and angiomata which give rise to profuse hemorrhage either spontaneously or as a result of trauma. We have recently had the opportunity to study three different families, all of which showed several members similarly affected. All suffered from repeated, severe epistaxes, the most frequent complication of the disease. One patient also had multiple pulmonary arteriovenous fistulae, which is another frequent complication.

FAMILY 1.—A 28-year-old, white unipara in the last trimester of an uncomplicated pregnancy was admitted to the U. S. Army Hospital, Landstuhl, Germany, on Jan. 22, 1955. Her admitting diagnosis was congenital heart disease, cyanotic type. She recalled being slightly cyanotic since early childhood, but since the age of 12, the cyanosis had not been as apparent. She denied ankle edema, chronic cough, and hemoptyses, but as long as she could remember there had been moderate exertional dyspnea, which was more evident with her pregnancy. Clubbing of her fingers and toes since early youth had been present, and during preceeding 10 years, pinpoint red spots had appeared on her lips. At the age of 13, severe epistaxes began, occurring at times almost daily and lasting from 10 to 15 minutes. A submucous resection in an attempt to control the nosebleeds was performed elsewhere in 1950. She had had three subsequent admissions to different hospitals for severe epistaxes requiring transfusions. On at least two other occasions iron therapy was required. There was no history of bleeding from any other site. Her family history revealed that a 31-year-old sister had had frequent nosebleeds since late childhood. She was not known to be cyanotic or to have pulmonary symptoms.

Pertinent physical findings included mild cyanosis, moderate clubbing of the fingers and toes, and 1-2 mm. multiple angiomata of both upper and lower lips, with a few similar lesions on the tongue and the distal one-third of the phalanges of both hands (Fig. 1). The precordium was symmetrical, the P. M. I. was in the fifth I. S. at the left midclavicular line, and there was an easily palpable systolic thrill which was maximal in the second right interspace. The heart was not enlarged to percussion. On auscultation a long, Grade 2, rough, systolic murmur was heard over the precordium, but loudest over the area of the thrill. Nasal examination revealed telangiectases of the mucosa of Little's area bilaterally. The hemoglobin was 12.5 gm. per 100 cc., and the hematocrit was 38%. The red cells were hypochromic and microcytic. Chest roentgenogram and cardiac fluoroscopy revealed a normal-sized heart with aneurysmal dilatation and marked overactivity of the right pulmonary arteries with notching of the ribs on the right (Fig. 2). The electrocardiogram was normal.

Fig. 1.—Notice the multiple 2-3 ml. angiomata of the lips.

The presence of multiple small angiomata, predominently involving the lips, and a family history of nosebleeds substantiated the diagnosis of familial hemorrhagic telangiectasia. The physical findings of cyanosis with clubbing and a harsh systolic murmur and thrill over the area of the aneurysmal dilatation of the right pulmonary artery permitted the clinical diagnosis of associated arteriovenous fistula of the lung. The patient was returned to the United States, and at Walter Reed Army Hospital, Washington, D. C., angiocardiograms demonstrated an arteriovenous fistula in the right

Submitted for publication March 19, 1956.

Fig. 2.—There is a smooth lobulated mass at the right hilus. At fluoroscopy, it actively pulsated. With the Valsalva test, it decreased in size. Notice that the right 5th, 6th, and 7th ribs are notched and the heart is normal in size.

Fig. 3.—Angiocardiogram (courtesy of Colonel Mattingly, Walter Reed Army Hospital). The right hilar mass is filled with dye. There is no apparent afferent and efferent vessel because of proximity to the hilus. There is also a smaller fistula in the left lower lobe, which was obscured by heavy breast shadows on a routine posteroanterior chest film.

upper lobe as well as a small, unsuspected, one in the left lower lobe (Fig. 3).

Surgical exploration* of the right upper chest revealed almost complete pleural symphysis in which there were hundreds of small pleural vessels and a definite thrill in the anterior segment of the right upper lobe. This segment resembled a cluster of grapes with numerous, segmental, blood-filled channels. On compression of the dilated anterior segmental artery the thrill disappeared and the vessels in the involved lung collapsed. This portion of the right upper lobe was removed and was found to contain many large blood-filled and blood-dilated vessels with numerous communications between the anterior segmental artery and vein. There was a dramatic decrease in the patient's cyanosis, and her postoperative course was uncomplicated. It is planned that she will return to Walter Reed Army Hospital in three months for reevaluation and probable removal of her left lower lung field fistula. Her sister was examined because of the history of frequent nosebleeds and was found to have multiple telangiectases of the skin, but there was no evidence of pulmonary involvement.

Family 2.—A 56-year-old white woman was admitted to the U. S. Army Hospital, Landstuhl, Germany, on Feb. 4, 1955, because of recurrent nosebleeds with attending severe anemia. Her past history revealed the presence of recurrent severe nosebleeds since early childhood, varying from one every few months to several daily. In 1946, after several severe nosebleeds, multiple blood transfusions were necessary. During the year prior to admission she had epistaxes almost daily, usually awaking her in the early morning hours or shortly after arising. In 1952 a hemangioma on the midportion of the tongue was removed because of frequent bleeding. There was no history of bleeding from any other site.

On physical examination the only significant findings were a few 2-3 mm. angiomata over the lower lip, the hard palate, the left cheek, and Little's area of the nasal mucosa bilaterally (Fig. 4). Her initial hemoglobin was 6.4 gm. per 100 cc., with a hematocrit of 25%. The red cells were microcytic and hypochromic. The nasal bleeding was eventually controlled by using nasal packs, soaked with tetracaine (Pontocaine). Frequent applications of chemical cautery on a cotton-tipped applicator to the bleeding vessels were later effective. She has been followed for the past six months and has had only mild epistaxes on two

* Surgery was performed by Major E. J. Jahnke Jr. (MC), of the Walter Reed Army Hospital.

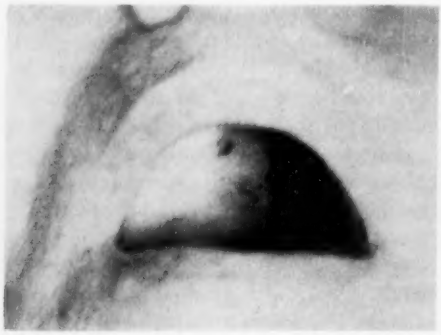

Fig. 4.—Notice the 4-5 ml. telangiectasia of the palate.

Fig. 5.—Notice the three 2 ml. angiomata of the lower lip and several telangiectases of the cheeks.

occasions. Her hemoglobin and hematocrit have remained with normal limits.

Family history revealed that her father and her only son both had had frequent nosebleeds since early youth. In neither was there a history of cyanosis, pulmonary distress, or bleeding from other sites. Her 33-year-old son was examined and gave a history of having had at least four to five moderately brisk nosebleeds weekly since the age of 8. Two years before he bled from the tongue. At the age of 15 the nasal mucosa had been cauterized to no avail. Physical examination was essentially negative except for a few small, 2-3 mm., red angiomata on both cheeks, the lower lip, and the buccal mucosa. Little's area of the nose was similarly involved bilaterally.

FAMILY 3.—A 35-year-old white man was admitted to the U. S. Army Hospital, Landstuhl, Germany, on March 15, 1955. For the last four years he had noted tiny red spots over the cheeks and lower lip and a few on the fingertips of both hands. During a similar period of time he had had nosebleeds three to four times weekly. The family history revealed that an older sister and his father had suffered from epistaxes as long as the patient could remember, although he was unaware of their having any similar skin lesions. Physical findings revealed two 5 mm. macular red lesions on the right cheek and lower chin, and three 2 mm. discrete, bright red angiomata on the lower lip and buccal mucosa (Fig. 5). The hemoglobin was 7.2 gm. per 100 cc., the hematocrit was 25%, and a blood smear showed microcytic, hypochromic red cells. In spite of nasal packs, which did control the serious episodes of epistaxes, he continued to have nosebleeds daily. His anemia was corrected by blood transfusions, and he was given ferrous sulfate daily.

Comment

The skin lesions are commonly seen on the face and mucosal surfaces of the lips, tongue, and mouth. The most typical cutaneous lesion is a small, 1-3 mm., punctiform, nonelevated, purple telangiectasis. There may be a marked photosensitivity of these lesions.[1] Visceral lesions are also frequently encountered, and the stomach, respiratory tract, uterus, kidney, bladder, meninges, brain, spinal cord, and eye may be involved. Hepatomegaly and splenomegaly are occasionally seen and may be due to actual liver telangiectases or posthepatic cirrhosis from multiple blood transfusions in the therapy of the secondary anemia due to epistaxes.[2] The presenting symptoms may be multiple and variable, with bleeding from any of these sites.

Repeated hemorrhages result in secondary anemia, chronic debility, and, if severe, death. The hereditary factor is apparently constant, and if not demonstrated, the failure is due to atavism.[3] It is detected in one-third of the members of the affected families. It is transmitted as a Mendelian dominant and affects both sexes equally. The condition was first described by Sutton, in 1864, and the subsequent reports of Rendu, Weber, and Osler established it as a clinical entity.[4] It is a well-known entity, as evidenced by the fact that 1451 cases were reported up to 1950.[5] The typical history consists of the onset of epistaxes in childhood and the development of multiple, reddish to violascious, cutaneous telangiectases which appear around the ages of 20-35 and usually increase in number as age ad-

vances. The occurrence of epistaxes, preceding by many years the development of visible telangiectases, is frequently seen. There may never be any discernible cutaneous telangiectases, and the diagnosis is easily missed, unless a family history of nosebleeds is elicited and nasal pharyngoscopy performed.[6] Smith and Lineback reported that there had been only two recorded instances involving the Negro race.[6] They reported a third instance in a Negro family and found nine cases in which the telangiectases were limited to the mucosa, five of whom were asymptomatic and never consulted a physician.

The histological picture usually reveals blood-filled spaces lined by a single layer of endothelium, surrounded by a thin layer of connective tissue, which explains why hemorrhages are so easily induced and at times so difficult to control.[6]

As more cases of pulmonary arteriovenous fistula were described, the fundamental relationship with hemorrhagic telangiectasia became apparent, and 50% of the patients with the former have shown cutaneous or mucosal telangiectases.[1,2,5-10] The classical clinical features of pulmonary arteriovenous fistula are the result of chronic anoxemia, due to the shunting of blood from the pulmonary arterial system into the systemic arterial system, and thus bypassing the pulmonary capillary bed. The degree of anoxemia is dependent upon the volume of the shunt as well as its duration. The cyanosis may not appear until late in life, as a result of progressive increase in the size of the shunt, and is usually out of proportion to the dyspnea. Secondary polycythemia occurs as a result of decreased oxygen saturation.

In addition to cyanosis, the common subjective symptoms are dyspnea, dizziness, faintness, palpitation, pain in the chest, headache, and paresthesias. If cyanosis is present, clubbing of the fingers and toes is usually present. Unlike peripheral arteriovenous fistula, the heart is usually normal in size because of the low pulmonary bed pressure. However, if the shunt is of great enough proportion, the heart may be enlarged. On auscultation there may be a bruit over the lung, which may be continuous, systolic, or diastolic in timing. The intensity of the murmur often increases on inspiration and decreases on expiration. Laboratory investigations will usually reveal polycythemia, elevated hematocrit, increased total blood volume, and decreased oxygen saturation of the peripheral arterial blood, which will further decrease with exercise. In contrast to peripheral arteriovenous fistulae, the increase in blood volume is due to increase in red cell mass and not increased plasma. Polycythemia may be absent as the result of frequent nasal bleeding. In as high as 50% of the cases, the classical described clinical picture will not occur. Under these circumstances it is even more important to pay particular attention to the characteristic roentgenographic findings. With rare exceptions, there will be an abnormal shadow in the lung fields. The characteristic shadow may lie behind the heart and be missed, but the usual finding is a lobulated, rounded mass with smooth, discrete margins with a predilection for the lower lobes. Connecting the mass with the hilum are two or more sinuous linear shadows, which represent the dilated afferent and efferent blood vessels. Fluoroscopy may reveal pulsations in the lesions and in the hilus on the same side. In about one-half of the cases there is a decrease in size of the vascular sac on performing the Valsalva test and an increase in size with the Müller test. Laminography and roentgen kymographic studies will often further clarify the vascular status of the round tumor of the lung.[7] Notching of the ribs in the area of arteriovenous fistula, as was found in our case, has not previously been reported. In 50% to 60% of the cases[8] there are multiple fistulae, and it becomes imperative to assess this properly prior to surgery. Four cases have been described in which the usual saccular dilatation was not present but instead numerous small telangiectases were present.[9] Thus, angiocardiography is indicated in every case

in which surgical treatment is contemplated. Small arteriovenous fistulae can be missed with the use of even the above diagnostic tools.

Symptomatic arteriovenous fistulae necessitates surgical excision. New fistulae may develop later, making it imperative that any surgery preserve as much lung as is possible. The asymptomatic patient with a small lesion must be kept under close observation if operation is deferred. He should be fully aware of the hazards to which he is thereby exposed, i. e., fatal pulmonary hemorrhage, intravascular clotting, brain abscess, and bacterial endarteritis. It is also important to follow these patients after surgery by hematocrit, hemoglobin, and peripheral oxygen saturation determinations. Multiple fistulae or cavernous changes in multiple areas of the lung on occasions may make surgery inadvisable.

The commonest symptom of the disease is recurrent epistaxis. Application of caustic agents, submucosal injection of sclerosing solutions, such as quinine, the use of hemostatic gauze as a nasal pack, ligation of the external carotid arteries, electrocauterization, and x-ray and radium therapy have all been tried and found lacking.[11,12] The use of rutin or estrogen has generally been found ineffective. However, Koch and co-workers [11] and Heyde [13] have found estrogen therapy in the female and estrogen-androgen in the male helpful. Their use would seem warranted if nasal bleeding is severe. The least traumatizing form of local therapy seems to work best. Whole-blood transfusions and iron replacement therapy are intermittently required.

Summary

The hereditary nature and skin lesions in each family were typical of the Rendu-Weber-Osler's disease. The telangiectases became apparent in the second and third decades. Severe, recurrent epistaxes, beginning in late childhood, was the only significant symptom, except for the young woman described in Family 1. The control of nasal bleeding is difficult, but the least traumatizing local therapy is the most effective. Hormone therapy may be useful in some of these patients.

The importance of thorough roentgenographic examination including angiocardiography to detect asymptomatic pulmonary arteriovenous fistula has been stressed. Previously unreported case of rib notching was noted in one patient with a large pulmonary fistula.

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Tumor Implantation at Paracentesis Sites

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Introduction

Factors determining the transplantability and rate of growth of tumors are many. Among these are the nature and degree of malignancy of the tumor tissue, responsiveness of the site of transplant to the new growth, the degree of trauma incident to the transplantation, and the nutritional status of the implanted area.

Surgeons have long been familiar with the distressing frequency of recurrence of tumors in operative scars [1] and have taken steps to amend their techniques so as to avoid this unnecessary complication.[2-4] When a tumor is inoperable or where removal is necessarily incomplete, the rate of regrowth following surgery has ofttimes been noted to be excessive, far outstripping the calculated growth rate prior to surgical intervention.[5] In such instances, the trauma of surgery perhaps favors rapid proliferation of cancer cells by upsetting whatever balance between growth and growth resistance was previously operative.

It has also been noted for some time that cancer cells injected into a new area of the human host will survive and metastasize. Primrose [6] reported the appearance of tumor in the breast and axillary glands following the submammary injection of ascitic fluid aspirated from a patient with ovarian malignancy in an attempt to immunize the patient against her tumor. While such a measure would not be undertaken today, the necessary procedure of abdominal paracentesis may, on occasion, offer an unavoidable opportunity to observe the rapidity of growth of transplanted tumor cells. The following three cases are illustrative.

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Report of Cases

CASE 1.—A 59-year-old white woman, whose mother had ovarian carcinoma and ascites, noted gradual abdominal enlargement, weakness, dyspnea, and weight loss over a three-week period in June, 1955. Physical examination revealed ascites, a tender mass in the right midabdomen, and a mass approximately 17 cm. in diameter occupying the right pelvis, depressing the uterus and extending medially.

On July 7, 1955, a laparotomy was performed at the Woman's Medical College Hospital on the Service of Dr. Mary DeWitt Pettit. Bilateral ovarian carcinoma was found as well as omental tumor infiltration. Both ovaries were removed. Postoperative therapy consisted of triethylene thiophosphoramide (Thio-TEPA)* given intravenously in two courses totalling 75 mg. through July, August, and December, 1955. One paracentesis was necessary during this period (July 26, 1955) and was done by placing a cannula in the posterior cul-de-sac and attaching a catheter, which was left in place to drain for one week and then removed.

The ascitic fluid slowly reaccumulated, but it was not until Feb. 14, 1956, that it became marked and the patient noted a firm, nontender nodule on the anterior chest wall at the ninth right costochondral junction. On Feb. 16, a paracentesis was performed, with removal of 4000 cc. of ascitic fluid, and 10 mg. of triethylene thiophosphoramide was instilled. Two more paracenteses were performed, Feb. 21 and March 6, with removal of 5600 and 3500 cc. of ascitic fluid. The ascitic fluid was positive for tumor cells on several occasions before and after instillation of triethylene thiophosphoramide.

* Thio-TEPA was supplied for clinical investigation by Dr. J. M. Ruegsegger, of Lederle Laboratories Division, American Cyanamid Company, to Dr. Carman C. Thomas, Director of Oncology, Woman's Medical College of Pennsylvania.

Fig. 1 (Case 1).—Tumor nodule at the site of a paracentesis six days previously.

Fig. 2 (Case 1).—Tumor nodule 30 days after paracentesis and 27 days after the instillation of 40 mg. of triethylene thiophosphoramide, showing definite reduction in size.

On March 12, a tumor mass measuring approximately 3 cm. in diameter was noted at the site of the tap six days previously. (Fig. 1). March 15, forty milligrams of triethylene thiophosphoramide was instilled into the peritoneal cavity, and thereafter the fluid did not reaccumulate in quantity sufficient to require paracentesis over a six-week period of observation. In addition, definite shrinkage of the tumor nodule at the side of paracentesis was observed (Fig. 2), as well as of the one on the chest wall. This response doubtless reflects the local as well as systemic cancercidal effect of the larger dose of triethylene thiophosphoramide.

CASE 2.—A 66-year-old white woman was admitted to the Woman's Medical College Hospital on April 6, 1955, with anorexia, occasional vomiting, and ascites. An abdominal paracentesis was performed on April 8, with removal of 5525 cc. of fluid, reported negative for tumor cells. Nine days later, an "induration" was reported at the site of paracentesis.

On May 3, the patient underwent laparotomy, and a papillary cystadenocarcinoma of the right ovary with metastasis to other pelvic organs and pelvic serosa was found. In the abdominal wall at the site of previous paracentesis a tumor implant formed a hard nodule approximately 4.5 cm. in diameter. Following surgery a course of roentgen therapy to the abdomen and pelvis was given from May through June, 1955. Subsequently, the patient received intraperitoneal colloidal Au^{198} and over a four-month period required four paracenteses and two blood transfusions.

She died on Oct. 30, 1955, six months after the onset of symptoms.

CASE 3.—A 46-year-old white woman had a carcinoma of the sigmoid colon resected with anterior anastomosis on July 12, 1954, at the Graduate Hospital of the University of Pennsylvania. The tumor extended through all layers of the bowel but had apparently not metastasized. At the same time a large myoma of the uterus was enucleated. A

year later the patient noted abdominal discomfort, distention, and some tenesmus. On Sept. 16, 1955, a paracentesis was attempted but was unsuccessful, the patient becoming weak and pale during the procedure.

The following day a successful paracentesis yielded 7775 cc. of bloody fluid. Nine days later 6000 cc. of cloudy yellow fluid was removed, a cell block of which was negative for tumor cells. Following paracentesis, a mass could be palpated in the left lower portion of the abdomen, and on Oct. 3, seventeen days after the first attempt at paracentesis, laparotomy revealed a large tumor of the left ovary, measuring 25×10×10 cm., extending across the pelvis and adherent to the cecum and anterior abdominal wall. An area of metastasis was noted in the liver. In addition, tumor tissue measuring 6 cm. in diameter was found implanted on the parietal peritoneum of the anterior abdominal wall at an area 4 cm. below the umbilicus, the site of the first paracentesis. In retrospect, it was assumed that at the initial unsuccessful attempt at paracentesis the ovarian tumor was traumatized, with subsequent bleeding and dissemination of tumor cells throughout the ascitic fluid.

Comment

Much cancer research today is facilitated by the factor of transmissability of human tumors to certain experimental animals under controlled conditions. The anterior chamber of the rabbit's eye and the hamster's cheek pouch have been found to be good tumor recipients, and the use of cortisone [7] and sometimes the accompaniment of embryonic tissues [8] facilitates the transplantation. That this heterologous transfer is possible bespeaks the tremendous capacity of tumor cells to survive and makes understandable their ability to seed themselves easily on areas of trauma in their host.

Early reports of tumors developing at the sites of paracentesis appeared in the European literature,[9] and since then, the phenomenon has been observed sporadically by others.[10] In the majority of cases reported and those herein presented, the tumors responsible for the ascites and the implants have been primary in the ovary.

Of intra-abdominal neoplasms, those arising in or metastasizing to the ovary [11] are conspicuous both for the early production of ascites and for following, for a time at least, a more attenuated course after metastases and extension have occurred. The average survival time of cases of inoperable ovarian carcinoma is 18 months, which compares favorably with that for rectum (14 months), pancreas (12 months), and liver (3.2 months).[12] As in the ascites tumor of mice, the peritoneal fluid of metastatic ovarian carcinoma is usually rich in tumor cells, and frequently clusters and rosettes are observed, resembling the histology of the primary lesion.[13] However, the absence of tumor cells in cases with obvious peritoneal implantation is frequently reported and is probably related to mechanical factors concerned in the collection and handling of the specimens.

Whatever the primary tumor, the transplantation of viable cells in the abdominal cavity is facilitated by injury, as observed both clinically and experimentally.[14] The three cases herein presented illustrate that sizable tumor nodules may occur on the abdominal wall 6, 9, and 17 days after the trauma of paracentesis. The growth rate of such transplants is not necessarily the same as that of the primary tumor, but may be extremely rapid. Whether this variation in growth rate is related to alterations existing at a site of trauma can only be postulated.

Summary

In abdominal carcinoma with ascites, particularly secondary to ovarian neoplasms, the occurrence of sizable tumors developing rapidly by implantation at the sites of paracentesis is not unusual. Three cases are presented in which tumor nodules measuring 3, 4.5, and 6 cm. in diameter developed in the abdominal wall 6, 9, and 17 days following paracentesis. The background and mechanism of this phenomenon are briefly reviewed.

Dr. Mary DeWitt Pettit, of the Woman's Medical College of Pennsylvania, gave permission to report her case, and Mr. Paul Hoffman gave photographic assistance.

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News and Comment

ANNOUNCEMENTS

Center for Aging Research.—Establishment of a Center for Aging Research in the National Institutes of Health has been accomplished.

Dr. G. Halsey Hunt, formerly associate chief of the Service's Bureau of Medical Services, was appointed director of the Center. He assumed his duties on Nov. 19.

The new Center is a part of the Public Health Service's program to coordinate and accelerate all of its activities in the field of aging. In the Office of the Surgeon General, these activities have been placed under the direction of Dr. John W. Porterfield.

The primary objective of the new program is to encourage and support additional research into the mechanisms involved in aging. The program will assist universities and other research institutions in establishing a broad research program which will bring the full range of biological, psychological, and social sciences to bear on the problem. A first activity will be to aid universities, medical schools, and other research organizations in establishing comprehensive research centers on aging, to be supported in part by research grants from the National Institutes of Health.

"The Public Health Service has long been concerned with the health problems of our aging population," Dr. Burney said. "Our Bureau of State Services supports State and local health departments in restorative services for the aged. The major portion of the Service's research efforts in the field of aging has been largely centered in the National Institutes of Health, which at present is expending about $2 million in its own research activities and in grant support of projects directly related to aging."

Creation of a Center for Aging Research in the Public Health Service is in line with the program developed by the Federal Government through the Federal Council on Aging and the member departments and agencies to coordinate all activities associated with the problem of aging. The new Center will more effectively coordinate research activities in aging and will stimulate the additional research that is urgently needed to obtain solutions to the serious problems presented by the aging of the population.

Director of the new program, Dr. Hunt, is a native of Newton, Mass., and a graduate of Brown University and of Columbia University College of Physicians and Surgeons. He served his internship and residency in surgery at Presbyterian Hospital, New York, and after four years in private practice was commissioned in the Regular Corps of the Public Health Service in July, 1936. He served on the surgical staffs of Public Health Service Hospitals at Staten Island, N. Y.; Seattle; San Francisco, and Louisville before coming to Washington in 1945. He has been assistant chief and chief of the Division of Hospitals which administers the Public Health Service hospital system and since 1952 has been associate chief of the Bureau of Medical Services, which encompasses the hospital system as well as other medical care and related activities of the Service. Before and during his career in hospital administration, Dr. Hunt has been responsible for numerous studies of private medical group practice, for hospital surveys, and for evaluations of the needs for medical facilities and care.

Dr. Hunt is a member of the Board of Governors of the American College of Surgeons and is first vice-president of the Board of Trustees of Medical Service of the District of Columbia.

The Seventh International Cancer Congress will be held in London, England, July 6-12, 1958, under the presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress: (*a*) Experimental; (*b*) Clinical and Cancer Control.

Special emphasis will be placed on Hormones and Cancer, Chemotherapy, Carcinogenesis, and Cancer of the Lung.

Proferred papers will only be considered if submitted with an accompanying abstract (not over 200 words) before October, 1957, and if dealing with new and unpublished work.

The registration fee for the Congress will be £ 10 or $30, and the latest date for registration without late fee will be Jan. 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to one of the following: The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2, England; J. H. Maisin, President, Union Internationale Contre Le Cancer, Voer des Capucins, 61, Louvain, Belgium; Harold Dorn, Secretary General, Union Internationale Contre Le Cancer, National Institute of Health, Bethesda 14, Md., U. S. A.

GENERAL NEWS

Nursing Homes and General Hospitals.—The first nationwide report on the geographic distribution of nursing homes and general hospitals providing skilled nursing service has been completed by the Public Health Service, Department of Health, Education, and Welfare.

The survey included 564,826 beds in 5200 general hospitals and 171,106 beds in 6531 skilled nursing homes.

In 71 greater metropolitan counties there are 4.1 general hospital beds and 1.3 beds in skilled nursing homes for every 1000 population. In 896 isolated rural counties with no incorporated community of 2500 or more there are 1.8 general hospital beds and 0.4 beds in nursing homes which provide skilled nursing services for every 1000 people, the survey shows.

The supply of beds in general hospitals and skilled nursing homes in counties tends to increase in accordance with per capita income, the study indicates. The number of skilled nursing home beds also tends to increase with the proportion of people who are 65 and older, but the number of general hospital beds shows no relationship to the number of older people. On the average, there are more general hospital beds and skilled nursing home beds in counties with relatively large numbers of doctors and nurses.

Patterns revealed by the study are discussed by the authors, Jerry Solon and Anna Mae Baney, in an article in *Public Health Reports* for October, 1956. The complete study, entitled "General Hospitals and Nursing Homes: Patterns and Relationships in Their Geographic Distribution," was published as Public Health Monograph No. 44 (Public Health Service Publication No. 492) and may be purchased from the Government Printing Office, Washington, D. C., for 40 cents.

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

The Collected Papers of Wilfred Trotter, F.R.S. Price, $3.50. Pp. 194. Oxford University Press, Amen House, Warwick Sq., London, E. C. 4; 114 Fifth Ave., New York 11, 1941.

*Two of Trotter's pupils, Sir Francis Walshe and Mr. Julian Taylor, and Trotter's son, Dr. W. R. Trotter, provided material about his personal and professional life. Taylor's Presidential Address given at the Meeting of the Surgical Section of the Royal Society of Medicine on Nov. 3, 1948 (**Univ. Coll. Hosp. Mag.** 34:105-116, 1949) may be consulted for further details.*

On our side of the Atlantic we are not as familiar as we ought to be with the medical philosophy of that great Englishman, Wilfred Trotter (1872-1939). This is a reason to examine here a book of his essays which appeared so long ago as 1941. "The Collected Papers of Wilfred Trotter" are made up of nine addresses, a paper, and two letters to *The Times*, forwarded by his son, Dr. W. R. Trotter. The papers are delightful reading, and they form a continuing source of inspiration for those who have become familiar with their thought, wit, and charm, to say nothing of their impeccable English. One could wish for American medicine nothing better than that Trotter's writings should get a wide currency here.

Trotter was Professor of Surgery at the University College Hospital in London at the time of his death, in 1939. In his later years he had relinquished a large private practice to take this whole-time post. This of itself, while unusual, would not have made him unique. As a young man, while Surgical Registrar at the University College Hospital (1901-1904), he had begun writing in his off hours the justly famous essay in social psychology, "Instincts of the Herd in Peace and War" (Unwin, London, 1916, 213 pages). Meanwhile he developed into one of the world's most technically proficient surgeons and an acknowledged master of literary medicine.

Since Trotter is virtually unknown to Americans, it may be helpful to introduce him by way of one who had been his student and, later, his colleague and friend. The remainder of this paragraph is constructed out of discussions with Sir Francis Walshe. Trotter was a brilliant clinician and operative surgeon, and a man of immense judgment. He earned his living as a surgeon, but surgery was but one side—and that not the major—of his intellectual activity. He was a philosopher in a profession where there are none. He was an omnivorous reader on all subjects. With his colleagues he was universally popular and became a legend in his latter years. His influence on British medicine was quite phenomenal, and his death in his sixties was a sad blow. He was the most courteous and modest of men; he declined all the public honors and titles he might have had, and eschewed publicity. Trotter was English of the English. He never left the country, and visiting Americans rarely saw him, and few indeed even knew of his existence. He was very elusive, and only those who knew him saw the best of him. He had a penetrating sense of humor, and his keenest shafts never really wounded; they were so completely empty of malice. Altogether he was a man who it was a rare privilege to know.

What is of great importance for us today is the clear thinking that Trotter brought to some vital problems that continue to beset medicine. Perhaps of even greater moment, now that we are oppressed by reams of turgid writing—light-heartedly termed "the literature"—was Trotter's absolute mastery of English. For those with literary inclination he is a model of thought and form. Trotter is said to have quoted George Meredith, sharing this author's literary ideals, that every word be selected for exact meaning and emphasis, and then be set into a place where it fit. Trotter also admired Robert Louis Stevenson's adjectives, similes, and his careful though apparently light-hearted construction. Trotter's expression

reminds one of Lincoln in its simplicity, its honesty, and in its penetration. Both had the Biblical touch without the repetitiousness.

These essays are remarkable in their compactness. The sentences are usually short and vigorous, and their meaning clear. To have heard them must have been a rare treat. Their reading, however, requires considerable attention, since the sentences say so very much, and one cannot hear the shadings and the emphasis. Yet many of Trotter's paragraphs can stand alone, lifted from context, and point a lesson. The medical editor needing "fillers" could draw on this erudite little volume for years and hardly exhaust the material.

The opening essay, on "Emergencies," is surely one of the most beautiful statements ever to be made on this elusive topic. In some dozen pages Trotter developed the theme that character, matured power of judgment, and grasp of fundamental principle are more important in emergency than are detailed knowledge and executive skill. He pointed to the uses and abuses of the natural process with epistaxis as a concrete example. (Hardly one physician in ten will know about his method of halting nasal bleeding, probably as infallible as all other methods combined.) As in all of his writings, there are little asides, a flash or two of free association or parenthetical thought, where Trotter turned a piquant light on an interesting or important point. His writings abound with wonderful insights; there is such a feast of them that it is hard to know which of his essays to single out in this regard.

In his consideration of emergency, Trotter discussed the duties and privileges of the physician and his place in the social structure where he rated the profession among the small class that can still be called jobs for men. "When I speak of jobs for men," he said, "I use a traditional phrase that nowadays needs a little definition. By it I mean professions in which it is possible for people—men or women—to pursue the dying ideal that an occupation for adults should allow an intellectual freedom, should give character as much chance as cleverness, and should be subject to the tonic of difficulty and the spice of danger." Here the word danger was not used in an ordinary sense but rather as an index "of the inherent difficulty and instability of the relation of patient and doctor."

In "The Commemoration of Great Men," Trotter examined the life and work of John Hunter to point up the motives of hero worship and to tell why men achieve greatness after they are no longer here to savor it. "After he is dead and when we are freed from the distraction of the actual presence which unhappily tends so often to be odd, angular, and even quarrelsome," it isn't so difficult to recognize greatness. But our feelings impede the free transmission of his ideas be he alive or dead, as Trotter said: "discoverers of new truths *always* find their ideas resisted."

It is impossible to catch in a review the fire of this great Hunterian Address which is in the best style of Trotter's maturity. His familiarity with the uses of the later-day psychiatry afforded this medical philosopher another vantage point from which to comment on the cultivation of "the delicate art of handling ideas." It has been said of Trotter that he learned the German language to be able to read Freud in the original.

In "A Landmark in Neurology," an address delivered before the Royal Society of Medicine, he commemorated Godlee's pioneer operation for a tumor of the brain, performed at the National Hospital for Epilepsy and Paralysis on Nov. 25, 1884, and characteristically he did not forget the tragic role played by the young patient. He added the name of Henderson "to the exiguous role of those by whose misfortune or endurance the world has directly gained. . . . It is a strange defect in medical history to have kept so few of the names of these benefactors and to have left it to accident that we still know there existed such humble but significant people as little James Phipps and Sarah Nelmes or Alexis St. Martin. To the high professional spirit treasuring such names may seem trivial and even a little ludricrous. Let us not forget, however, that they are the names of those who have borne more substantial witness than has yet been produced by any philosopher or any theologian that all suffering is not in vain."

He delivered the second Victor Horsley Memorial Lecture on July 9, 1926, a decade after Horsley's death, when he spoke about "The Insulation of the Nervous System." Here he examined the importance to the vertebrate organism of the maintenance of neural insulation, an idea that still could use some attention.

Before the Anthropological Society of University College, London, he developed an interesting thesis in a lecture on "The Functions of the Human Skull," indicating that uprightness has freed the skull from offense and defence and more importantly freed the brain for autonomy.

The address delivered at the opening session of the University College Hospital Medical School in 1932, entitled, "Art and Science in Medicine," is perhaps the gem of the sparkling lot. For me, this is the most compelling statement ever to be made on this overworked topic. Trotter's words to the student body on the aptitudes of the good doctor are pure poetry, and if they did not elicit an extrasystole or two, or a catch in the throat, or water the eyes a bit, in the student who heard Trotter's delivery then,

"The motions of his spirit are dull as night,
And his affections dark as Erebus."

Such insight, simplicity, and absolute honesty expressed in such concord of sound I have nowhere else experienced in any physician writer.

The only essay in this book which evidently was not given as a lecture is reprinted from the *British Medical Journal* (1930) and is entitled, "Observation and Experiment and Their Use in Medical Sciences." Here Trotter examined the uses of clinical observation and noted that it has never been a very effective instrument for penetrating the fundamental secrets of health and disease except in the hands of an occasional genius. Then experiment steps into the breech. Both have their uses and neither can afford the luxury of deprecating the other. In this paper he was working toward a theory of medical knowledge. It is in this essay that he dropped the interesting aside that the apparent necessity for the medical student to complete his knowledge of the normal before beginning his study of the abnormal is probably as fallacious as it is practically wasteful and inconvenient.

Trotter wrote the final essay entitled, "Has the Intellect a Function" when his blood urea nitrogen was well over 100 mg. per 100 cc.; his death occurred some six months later. Here he was thinking about the problem of how the human mind might be made into an instrument of greater practical use. In it he demolished the concept of pure reason and pointed to the devastatingly powerful emotions as prime movers. As he said: "We can tame them a little—only perhaps to make them more insidious—but even in the most dispassioned train of reasoning, they are apt to exercise a steady treacherous pressure." This formulation was mainly a result of his own work of some four decades, beginning with ideas that led to his book on "The Herd Instinct."

The last paragraph of this final address delivered to the students of St. Mary's Hospital may be cited as an illustration of the simplicity of his style and a sample of his humor. "We like to suppose ourselves easily receptive to the new, and that we are so by virtue of a natural mechanism. Unfortunately this is the exact opposite of the truth. The mind likes a strange idea as little as the body likes a strange protein, and resists it with a similar energy. It would not perhaps be too fanciful to say that a new idea is the most quickly acting antigen known to science. If we watch ourselves honestly we shall often find that we have begun to argue against a new idea even before it has been completely stated. I have no doubt that that last sentence has already met with repudiation—and shown how quickly the defence mechanism gets to work."

The few excerpts cited in this review show how Trotter's polished prose very nearly conceals the art of its composition. Those who knew him well tell us that all of his addresses were prepared with the greatest care, with long consideration and repeated writing. Perhaps this accounts for the perfect choice and use of words, with exact meanings, though he never fell into the common error of making words more important than the matter.

One of Trotter's colleagues has remarked that to commend his fastidious and faultless art of writing and speaking, however piously, is an unnecessary intrusion. This may hold for the British scene, where Trotter is known and where he has become a legend. I do not believe it applies in the United States, where Trotter is largely unknown and where perhaps his work might have its greatest impact in the future. It may be noted that his scientific papers chiefly on skin sensation, subdural hematoma, head injuries, and malignant disease of the pharynx are as profound in their way as those on the philosophy of medicine.

Finally, it may occur to others to wonder why modern medicine's greatest philosopher was a surgeon. He is said to have been influenced by the fact that at the time of his qualifying, surgery was the "growing-point" of the medical sciences. He was undoubtedly influenced by certain of his teachers, particularly Sir Victor Horsley. Had he qualified in the suceeding generation, it is likely that he would have taken to internal medicine, as he once casually remarked to one who knew him intimately.

In summary then, the book entitled "The Collected Papers of Wilfred Trotter" is without doubt one of the classics of modern medicine. No physician, particularly if he be of reflective bent, can afford to ignore this book. It is the product of one of medicine's finest minds, at once one of its very rare philosophers and a truly great physician and surgeon. For the physician with a need to be heard, there is no better model to emulate. If this were not sufficient, the collected writings of Trotter are quite delightful reading. Not to know about them is to be deprived of some of the greatest stimulation that has ever graced what may be with truth termed the literature of medicine.

CHARLES D. ARING, M.D.

Klinik der einheimischen Infektionskrankheiten. By Professor Dr. W. Grunke. Price, DM 51, 60. Pp. 620, with 177 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C. 1.

The author emphasizes in the preface that he did not intend to describe and discuss the infectious diseases so thoroughly as in the German "Handbook of Internal Medicine," but to present the facts of general importance to the practitioner. Therefore, controversial problems and theoretical bacteriological or serological findings are omitted or briefly described, inasmuch as the author provides the reader with such a wealth of personal war and after-war experiences that the limitation to clinical observations is fully justified. The classification is original and deviates from the customary European and American differentiation. He divides the main chapters into the exanthematous diseases, the septic-typhoid group, infectious maladies with predominant localization in single organs (tonsillitis, pneumonitis, dysentery, hepatitis, encephalitis, meningitis, erysipelas, tularemia, cat-scratch disease, etc.), finally infectious diseases characterised by manifestations in various organs, such as toxoplasmosis, Coxsakie virus, and infectious mononucleosis. Such classification is disputable, and not everybody will approve that typhus fever is described under exanthematous diseases, typhoid fever, virus influenza, psittacosis, malaria under typhoid-septic diseases, and the Stevens-Johnson syndrome under epidemic stomatitis. The great value of this comprehensive book lies in the clearness of observations, that is enhanced by the excellent partly colored pictures with a few exceptions (diphtheric angina, chicken pox, typhoid roseola). The American literature is adequately considered, and for the foreign reader who knows the German language, the problem of geographical frequency of infectious diseases is particularly fascinating. The Medical school of Halle, where the author is Head of the Medical Department, is in the Prussian zone. The excellent chapter on typhoid fever, with fever curves and tables on remission intervals, comprises 60 pages, the section on virus pneumonia not even 1½ pages, the chapter on diphtheria describes excellently the technique of tracheotomy and intubation, but discusses the active immunization from a statistical viewpoint without any emphasis on the public health requirement. Likewise, the drug treatment of pertussis is described just as meticulously as in our textbooks of 1930, and the dangers of active immunizations are almost more emphasized than the advantage. However, such comparisons do not intend to express a criticism. Our present generation in this country is fortunately deprived of the opportunity to observe many diseases that are so well described in this textbook. But infectious diseases should not fade into oblivion, since epidemics may appear periodically in spite of immunizations and make the revival of forgotten knowledge very urgent.

WERNER GOTTSTEIN, M.D.

Sir William Gowers 1845-1915, A Biographical Appreciation. By Macdonald Critchley. Price, not given. Pp. 118, with 11 illustrations. William Heinemann, Ltd., 99 Great Russell St., London, W. C. 1, 1949.

That Gowers was the greatest clinical neurologist of all times many English-speaking colleagues of the author would be likely to agree. William Gowers was born in 1845, in Essex, in the eastern environs of London. Orphaned by the loss of his father, a shoemaker, at the age of 11 years, he achieved a fine scholastic training by means that are largely unknown. Apprenticed for two years to the local medical practitioner, Dr. Thomas Simpson, of Coggeshall in Essex, his industry was such that he appears to have learned not only the rudiments of the practice of medicine, and studied for and passed the London matriculation (1863), but at the same time furthered his general education particularly in literature, precise expression, languages, mathematics, botany, and, among other things, shorthand. It was at

this time that he began a shorthand diary; shorthand was to be an abiding interest throughout his professional life; it served him well in his recordings, much of which appeared in his voluminous publications. It is of some interest that those of his works that have not been disseminated are largely untranscribed in the shorthand script, in obscure and out-of-print journals.

In September, 1863, Gowers entered the University College Hospital as a medical student. He took his M.R.C.S. in 1867. His merits as a student were reflected in his appointment as assistant and secretary to Sir William Jenner, Bart., President of the Royal College of Physicians, a post which brought him in intimate contact with many of the leading men of medicine in Great Britian. He worked with Jenner until 1870, taking the M.B. (Lond.) with first-class honors in 1869.

It appears that Gowers' interest in the growing field of neurology was awakened by teachers at University College, including Sir Russell Reynolds, who had recently assisted in the founding of the National Hospital for the Paralyzed and Epileptic in Queen Square, and Charlton Bastion and Edward Sieveking. In 1870 Gowers secured the newly made appointment of Medical Registrar to the National Hospital. It was in this unique institution that he spent most of the remainder of his productive career. Here it was that he became intimately associated with a goodly share of the world's great in the then burgeoning neurological field, led by that noble figure, J. Hughlings Jackson, who was but ten years his senior. In only a few years he was launched into his career as an original thinker, a surpassing clinician, lecturer, and teacher; as the latter he functioned—and still functions via his fluent writings—as an instructor of the interested everywhere.

It is impossible to detail his many original and impeccable observations and his exacting description of them; they are succinctly described by Critchley. Perhaps it may serve in this regard to reprint one of Critchley's paragraphs describing the Gowers' method.

> "The formula of Gowers' contributions to neurology may . . . be described as the recognition of a number of salient, novel and important clinico-pathological features culled from his experience. These would be worked up and elaborated, and perhaps other cognate observations from the literature would be incorporated. In this way a short paper, or maybe a clinical lecture would take shape. This would then be published in one of the medical periodicals. Later the subject would be re-examined; modifications would be made, and new data added. Then the contribution would appear in book form, his publishers always being the firm of Churchill, and perhaps run to two or more editions. In this way Gowers secured a very wide audience."

In this manner many monographs were constructed, among the most famous in our day are the "Borderlands of Epilepsy," a study of a host of paroxysmally occurring disorders, on many of which after a half century he has still said the latest word. He was perhaps the outstanding exponent of the ophthalmoscope at the time his treatise on "Medical Ophthalmoscopy" appeared in 1879. His three-hundred-page monograph, "Epilepsy," remains very much current; a bit more than a decade has passed since William Lennox characterized this book as "the best thing on epilepsy which has been published." Yet, as was his wont, he delivered the substance of this monograph in the Gulstonian Lectures before the Royal College of Physicians of London as long ago as February, 1880.

For us in the midtwentieth century, all of his gems are in the shadow of that magnum opus, the great "Bible of Neurology," in two volumes entitled "Manual of Diseases of the Nervous System." The first volume appeared in 1886, the second in 1888. This was the most ambitious monograph on nervous disorders that had ever been attempted in any language. Into it Gowers poured all of his great neurological erudition and experience; he borrowed only meagerly from others. Except for a few photographs, even the illustrations were reproduced from his own drawings, at which he was quite adept. His concern with the proper use of language, as an instrument to say exactly what is meant, nothing more nor less, and to say it beautifully and with charm, is nowhere better illustrated than in his Manual. Almost without exception his many writings abound with material for quotation. As an example, "Tabes is a word which connotes almost nothing and so may be made to denote almost anything—a convenient characteristic in medical terminology," and again, "Our sensations transcend our vocabularies." It would be difficult to say too much for the

"Manual of Diseases of the Nervous System," volumes which none who fancy themselves neurologists should neglect in spite of the welter of textbooks that have followed. Perhaps a note about a Queen Square tradition "that anyone who thinks he has stumbled upon something new or obscure should not neglect to search Gower's Manual before claiming originality," will indicate something of its timelessness.

Critchley's biography is short—an interested reader can readily encompass it in an evening—however, it succeeds in recreating for us the origins of the National Hospital in Queen Square, and its nurture and development by Gowers and his colleagues. Much that might be helpful in understanding the genius of Gowers is missing, particularly from his formative years, but it is likely that this is nowhere available. The book is clearly printed on nonreflective paper; there are eleven illustrations, one of them an etching by Sir William himself. A valuable inclusion, occupying some eighteen pages, is a bibliography of Gowers' published work extending from the year 1872 through 1910. A careful index of four pages concludes this little volume by one of the National Hospital's many literate physicians. Formerly the Dean of the National Hospital faculty, Critchley remains a Senior Physician, a neurologist of fame, who himself has contributed to a continuing Queen Square tradition. Some of this tradition, a heritage from Gowers, Jackson, and their colleagues, consists of keen observation with a hawk-like attention to every detail of the patient's story and physical examination, together with painstaking recording; a prompt acquisition of a thorough experience with every disorder of the nervous system, and an exposition of all this in speaking or writing in a precise, graceful, and sparkling English. Here is an exposition of the subject that is wholly admirable from the neurological point of view. The mind's eye travels over the names of so many great men who have contributed to this unique present, but they remain unnamed for fear of omission. The debt for this approach is perhaps greatest to that "apogee of the great clinician," Sir William Gowers.

C. D. Aring.

Lehrbuch der inneren Medizin. Edited by Ludwig Heilmeyer. Price, 68 DM. Pp. 1326, with 241 illustrations. Springer-Verlag, Reichpietschufer 20, (1) Berlin W. 35, 1955.

With the first edition of this work, the famous "Springer Verlag" presents a new comprehensive text on internal medicine in the German language. It will have to compete with the work edited by Professor Denning and published by the "Thieme Verlag," which has become the standard text for the study of internal medicine in Germany during the last ten years.

Professor Heilmeyer is widely known as one of the key figures in Germany's postwar medicine. His special interests range from hematology to chemotherapy and cancer research. His literary production during the last few years has been somewhat phenomenal and includes a series of books.

In this present work, his special concern is the conflicting problem of ever expanding medical knowledge and comprehensive medical education. He believes to have found a new solution by selecting as authors assistants from his own medical clinic. In this way it should be possible to achieve together with unity and continuity of conception the best possible command and coverage of the material and to maintain the advantages of modern collaborative texts and avoid their disadvantages. One cannot entirely deny a certain element of logic in this conclusion. But after reading through several chapters of the work, one feels tempted to observe that reality may very well defy logic—and textbooks their forewords. The different chapters and sections appear less uniform and more unequal in competence and precision of presentation than texts written by a representative group of authorities not united by a single clinic.

Excellent presentations are the chapters on hematology, metabolism and infection, and renal diseases. The section on hematology gives a sound foundation of basic physiological and technical principles and covers all recent advances in our understanding of blood diseases, sorting critically significant facts and concepts from less important detail. The clinical pictures and syndromes are concisely and authoritatively described, as could be expected from its distinguished authors. Other excellent chapters include the ones on metabolism and endocrinology, by Dr. Weissbecker. The up-to-dateness of these sections is remarkable; the readable and lucid style of presentation comparing favorably with a great many other texts.

Relatively weak were the chapters on neurology and cardiovascular disease. The latter, especially, is full of anachronistic theories and contains some curious therapeutic sugges-

tions. Instances: Strophantin (Ouabain) is recommended for coronary insufficiency and vascular collapse as a prophylactic measure against congestive heart failure. The ultimate cause of cardiac insufficiency is uniformly seen in an inadequate oxygen supply and failing energy metabolism of the myocardium. Differing ideas are not discussed, and the implications of the foreward failure theory remain unmentioned.

A special note is created by a large chapter on psychosomatic medicine and psychotherapy. In the center of the presentation are problems of regulatory disturbances in the autonomic nervous system, which are based on concepts and theories of W. R. Hess. Problems of neurosis are presented in new lights of medical anthropology and existential philosophy. This chapter is brilliantly and stimulatingly written by G. Glauser, the psychotherapist of Professor Heilmeyer's clinic. His critical and evaluating attitude inspires confidence in his presentation of a subject where the separation of truth and fancy is so delicate and their line of demarcation sometimes imperceptible.

In summary then, with all advantages and disadvantages, this is an interesting and solid textbook of internal medicine, even if one fails to see in it a novelty in medical education.

HELMUT MUELLER, M.D.

Treatment of Migraine. By John R. Graham. Price, $4. Pp. 149, with 8 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

This pocket-sized book deals wisely and critically with one of the most vexing therapeutic problems in clinical medicine, the treatment of the patient with migraine. Its soundness and compassion reflect the author's wide experience with the disorder. In addition to containing an accurate and acute analysis of the coming and going of various drugs and programs for treating migraine, this book contains a number of interesting and little known historical facts about the disease. Anyone who has ever had a headache or who has to treat patients with headaches will profit by careful study of the book.

The price of this book, $4 for a small volume, may put it out of the range of many who should have it. Fifteen years ago a book of this size might have cost a dollar.

WILLIAM B. BEAN, M.D.

Praktische Gastroenterologie. By Dr. Ernst Hafter. Price, $11.45. Pp. 380, with 406 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1956.

This concise book holds more than its title promises; not only does it cover the entire field of gastroenterology in a very clear and thorough manner, but it also gives most valuable technical hints for x-ray examinations. The pictures (although all positives, probably for economic reasons) are outstanding in their instructiveness for the clinician. I'm sure, they are also a joy for the radiologist. I have read the chapters concerning "deformities of the gallbladder," "spontaneous rupture of the esophagus," and "jaundice" with exceptional pleasure. Any practitioner is bound to benefit by the authors' presentation of the "early diagnosis of carcinoma of the stomach," and it is also refreshing to read the latest about regional enteritis without political shadings. The surgical approach of perforated ulcer causes the reader to ponder whether the European technique of two-third stomach resection, done whenever possible, might not be sounder than the usual American way of tackling this emergency. Paper and bibliography are excellent. This is another Thieme book deserving translation into English.

ERICH STERN, M.D.

The Recovery Room: Immediate Postoperative Management. By Max S. Sadove, M.D., and James H. Cross, M.D., with contribution by 24 authorities. Price, $12. Pp. 597, with many illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

In 597 pages—divided into 21 chapters—Drs. Sadove and Cross have collected most of the data needed for building a recovery room and making it function. They clearly define a recovery room as being an intensive therapy center where acutely ill patients requiring more than average care are treated. This has led to the inclusion of medical emergencies as well as preoperative and postoperative surgical patients.

Chapter 3 (circulation, shock, and nutrition) contains about ninety pages which merit study by all surgical house staffs. The "Stir up Regimen" of cough, deep breathing, etc. is an example of how important phases of postoperative care are simplified and clarified so that even the novice can understand. Each of chapters four to twenty are presented by a separate surgical "specialist," who emphasizes the problems peculiar to his respective field—and this approach has here proved informative without the anticipated repetitions. Chapter twenty, on

medical problems, is complete and presented in a simple concise manner. It is an excellent guide for the surgical house staff.

Last, and certainly not least, is Chapter 21, on "Nursing Care in the Recovery Room." Intelligent, well-trained, and efficient nursing is essential for adequate patient care in the recovery room.

No criticism can be found in the content and manner of presentation of the material in this book. It should be found in every hospital library and be readily available for reference by all house staffs.

S. J. Fogelson, M.D.

Neuropharmacology. Transactions of the Second Conference May 25, 26, and 27, 1955, Princeton, N. J. Sponsored by Josiah Macy, Jr. Foundation. Edited by Harold A. Abramson. Price, $4.25. Pp. 328, with 85 illustrations and 26 tables. Josiah Macy, Jr. Foundation Publications, 16 W. 46th St., New York 36, 1956.

This book is the verbatim account of a three-day session, sponsored by The Josiah Macy, Jr. Foundation, to which were invited twenty-five clinicians and scientists in widely diverse fields. The common denominators were that each of the participants had some interest in the function of the brain and each was well known in his respective field. These fields ranged widely from neuroanatomy, biochemistry, psychology, and physiology to clinical and experimental psychiatry.

The sessions were mainly devoted to consideration of the psychosomimetic drugs and their relationship to schizophrenia. Five topics were presented by individual investigators, heavily interspersed with the comments, questions, and reflections of the other participants. The first paper covered the general field of lysergic acid diethylamide (LSD-25) and related compounds. The second topic dealt with the effects of various drugs on the behavior of both experimental animals and human beings. The third and fourth presentations were mainly related to experimental phychoses in human beings. The last session centered about the developments of tolerance to LSD-25 and a theory of the mechanism of experimental psychosis.

In general, the discussions were lively, informative and interesting—all of which made for a stimulating conference. However, the frequent interruptions, which enliven a conference, detract from the readibility and value of the transactions when printed in book form. I am of the opinion that it would be better to sacrifice "the informal nature of the meetings" in print and provide a book which has continuity of thought and expression of ideas. Finally, this book contains little of practical value or interest to the internist, neurologist, or psychiatrist except for the insight it provides into the current research revolving around the use of the psychosomimetic drugs.

Norman P. Goldstein, M.D.

Polysaccharides in Biology. Transactions of the First Conference April 27, 28, and 29, 1955, Princeton, N. J. Sponsored by Josiah Macy, Jr. Foundation. Edited by Georg F. Springer. Price, $5. Pp. 271, with 31 illustrations and 21 tables. Josiah Macy, Jr. Foundation Publications, 16 W. 46th St., New York 36, 1956.

In the preface it is said that the conferences of the Josiah Macy, Jr. Foundation are efforts to provide communication between investigators by means of small meetings with emphasis on discussion. The conference on polysaccharides appears to have fulfilled this purpose. The transactions are reported in a manner which preserves the spirit of spontaneous discussion, questioning, and rebuttal. Dr. Paul György was the chairman. There were twenty-seven members and guests.

In the transactions the first discussion, led by Dr. M. L. Wolfrom, is concerned with nomenclature. Among other things, the participants raise questions regarding application of the rules of carbohydrate nomenclature to the complex polysaccharides and consider such items as the use of desoxy- versus deoxy- as a prefix. The second discussion, conducted by Dr. Karl Meyer, is on problems of classification. A sample of this section is a question on the definition of mucopolysaccharides, which leads to several pages of contributions by various members on polydispersity and whether it is an artifact. The third part of the transactions, concerned with bacterial polysaccharides, is presented by Dr. Michael Heidelberger, with contributions in the form of discussion from various members of the conference. This chapter is ninety pages long, with inclusion of one hundred fifteen references. The fourth and last chapter records the discourse on blood group substances, by Prof. W. T. J. Morgan, whose main theme is the specificity of blood group characters, particularly those of the ABO system. This portion of the proceedings is one hundred seven pages long, including a list of eighty-nine

references. The deliberation includes discussions by various participants on such items as homogeneity of the substances, sources of and methods for isolating blood group substances, and also analysis by various means.

Although each of the participants in all the discussions had a chance to edit his remarks, the record of the proceedings has an air of verbatim reporting which adds to the feeling that each discussant spoke freely and objectively. This book contains perhaps the most recent work and opinions of the experts in its field.

ALFRED G. KARLSON, PH.D.

Cytology of the Blood and Blood-Forming Organs. By M. Bessis. Price, $22. Pp. 622, with 22 color plates and 404 figures. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

This represents an ambitious effort by one of the leading hematologists of France to cover the presently available methods of study relating to the morphology of the blood cells and bone marrow in a single book. In a volume of 622 pages, many of which are occupied by 404 figures and the bibliography, a prime need to insure the best possible success would seem to be the conservation of space. The reviewer feels that more essential text might have been included by omitting the discussion on collecting and preparing specimens of blood for routine examination and by omitting the discussion of the physiology and pathology of blood cells. All of this type of material has been well recorded many times and is easily available in other publications.

Additionally, and unfortunately, the volume is replete with uncritical and sometimes unacceptable statements, examples of which begin on page 4: "Only very rarely does the puncture of a bone fail to result in a specimen of marrow" (adequate specimen implied?); "puncture of lymph gland . . . enables a biopsy . . . to be avoided," and a statement later that "cells may not be obtained if the gland is sclerosed. Biopsy then becomes indispensable in certain cases" seems an inadequate qualification (page 179); "This disease (infectious mononucleosis) is difficult to classify cytologically because it is characterized by the appearance in the blood and in the lymph glands of mononuclear but pathological cells which have morphological characteristics intermediate between those of young monocytes and large lymphocytes. Most writers consider these to be abnormal monocytes . . ." (page 527). The pathologic cell in this disease has long been established as a lymphocyte.

On the whole, the translation of the original volume "Traité de cytologie sanguine" (copyright 1954 by Masson et Cie) appears very well done, although *des ganglions lymphatiques* will be more acceptable to American hematologists if translated as "lymph nodes" rather than "lymph glands."

A single volume designed as a synopsis of presently available techniques applicable to the examination of blood cells has much to commend itself to the interested student. However, this present work cannot be recommended without extensive revision.

BRUCE K. WISEMAN, M.D.

The Year Book of Endocrinology (1955-1956 Year Book Series). Edited by Gilbert S. Jordan, M.D., Ph.D. Price, not given. Pp. 367, with 72 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

This review of the year's literature in endocrinology reflects the brisk pace of the field. Work on steroid metabolism has led the field, but other categories have not been neglected. The book is divided into sections which include each endocrine gland as a subdivision plus sections on carbohydrate metabolism and endocrine treatment of neoplastic diseases. An introduction to each section is provided by the editor. The articles reviewed are presented as brief and unusually readable abstracts and are frequently followed by comment from the editor. These comments and the introductions to each section are a useful guide to reading.

Special articles by E. Perry McCullagh, on "Aldosterone," and L. Arthur Mirsky, on the "Hypoglycemic Action of the Sulfamide Derivatives in Diabetes Mellitus," give the book additional scope and together make it both recent and readable.

RICHARD F. HERNDON, M.D.

Fibrocystic Disease of the Pancreas. Report of Eighteenth Ross Pediatric Research Conference. Price, not given. Pp. 92, with illustrations. Ross Laboratories, Columbus 16, Ohio, 1956.

Fibrocystic disease of the pancreas, a chronic debilitation of infancy and early life, is characterized by disordered pancreatic function and chronic infections of the lung. It has

been a fascinating enigma for investigators ever since it was first described about two decades ago. This book is a copy of the transactions of the 18th Ross Pediatric Research Conference, which was held under the auspices of the Department of Pediatrics of the State University of Iowa, College of Medicine, at Iowa City, Sept. 30, 1955. Emphasis on genetics, embryology, endocrine function, particularly in fetal life, and the numerous disorders of various organ systems are discussed thoughtfully and in detail. Unfortunately, even the nature of the disease seems to have eluded physicians so far, though the nearest clue suggests that it is an example of an inborn error of metabolism. But whether one function or many simultaneously are disturbed is not clear. There are implications in this disorder for further understanding of the physiology of sweat and possibly such traditionally complicated problems as primary pulmonary emphysema in adults. Internists who are specially concerned with such problems would profit by reading this book, which has been edited thoughtfully by Dr. May and Dr. Frazier. By telling us how far we have gone in our understanding of this disease, they point even more clearly to how far we still have to go.

WILLIAM B. BEAN, M.D.

Ciba Foundation Colloquia on Ageing. Vol. II. Ageing in Transient Tissues. Edited by G. E. W. Wolstenholme and M. P. Cameron. Price, $6.75. Pp. 263, with 96 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Many biologists have hoped that a more direct attack on the problems of aging and senescence might be possible through study of "transient tissues." By transient tissues are meant such things as the placenta, the deciduous horns of animals, and corpus luteum, and other elements of ovarian tissue. These and a number of related topics are discussed learnedly and with a great deal of interest in this colloquium. Whether to consider erythrocytes as transient tissues was not settled, and in general surprisingly little use was made of information obtained from tissue cultures, which may still be the most hopeful of all approaches to the problems of aging. The essence of the question is whether aging represents a foreordained manifestation of doom with a fixed and limited potential written into the script at the time of birth or even long before or whether aging represents this process as it is modified by wear and tear, the buffets of everyday life, or unusual or very subtle influences in the direction of accelerating or speeding up the aging process. Perhaps even more important is whether aging can be delayed or prevented in part by manipulations of the external or internal environments, or both. For one who has not kept up with some of the biological aspects of aging as revealed in this symposium, the discussions are illuminating, the problems are presented clearly, and one winds up with an excellent measure of how desperately little is known about the process and how difficult are both the conceptual and the technical aspects and how hard it will be to achieve substantial progress along these lines. In a society which is aging and in which the domination is increasingly that of the older, conservative, and stereotyped, it is to be hoped that investigators young in attitude, if not in years, will continue to expand our still most meager knowledge of a problem which is central in the life and decline of every living thing. For a measure of our knowledge and a long view of the road this colloquium is fascinating if discouraging to read.

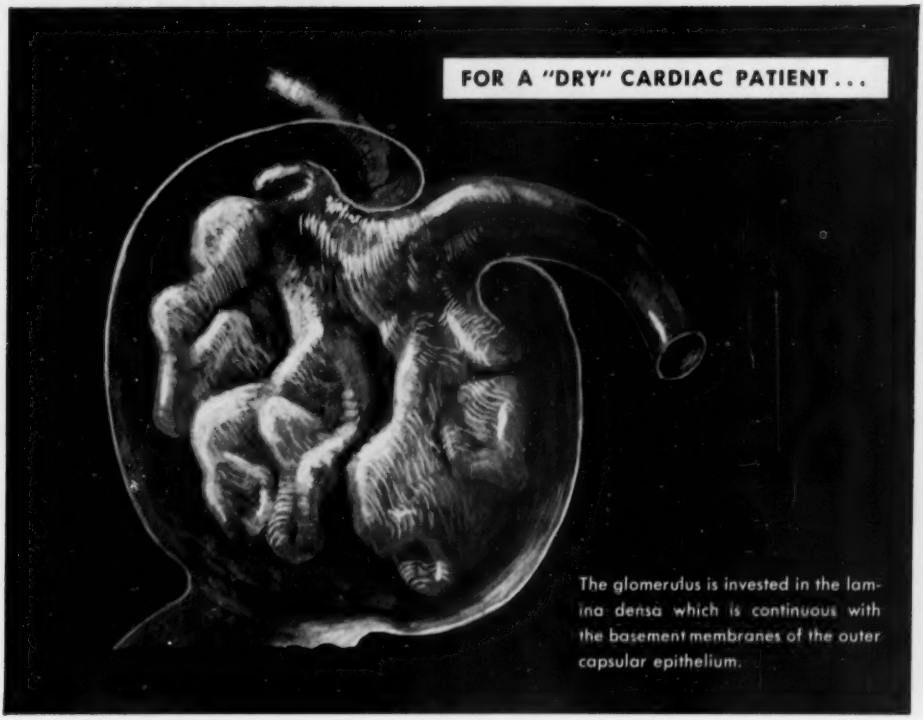
WILLIAM B. BEAN, M.D.

BOOKS RECEIVED

Proceedings of the Annual Meeting: Council for High Blood Pressure Research, American Heart Association, 1955. Price, $4.50. Pp. 186, with 61 figures and 12 tables. American Heart Association, 44 E. 23d St., New York 10, 1956.

The Image of the Heart. By Daniel E. Schneider, M.D. Price, $6. Pp. 267. International Universities Press, 227 W. 13th St., New York 11, 1956.

Psychologic Aspects in the Care of Infants and Children. Report of the Twenty-first Ross Pediatric Research Conference. Prepared by W. O. Robertson, M.D. Price, not given. Pp. 96, Ross Laboratories, Columbus 16, Ohio, 1956.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Research in the Service of Medicine.

1. Settel, E.: A Clinical Evaluation of a New Oral Diuretic, Rolicton, Postgrad. Med., Feb. 1957, in press.
2. Goldner, M.G.: Personal communication, June 29, 1956.

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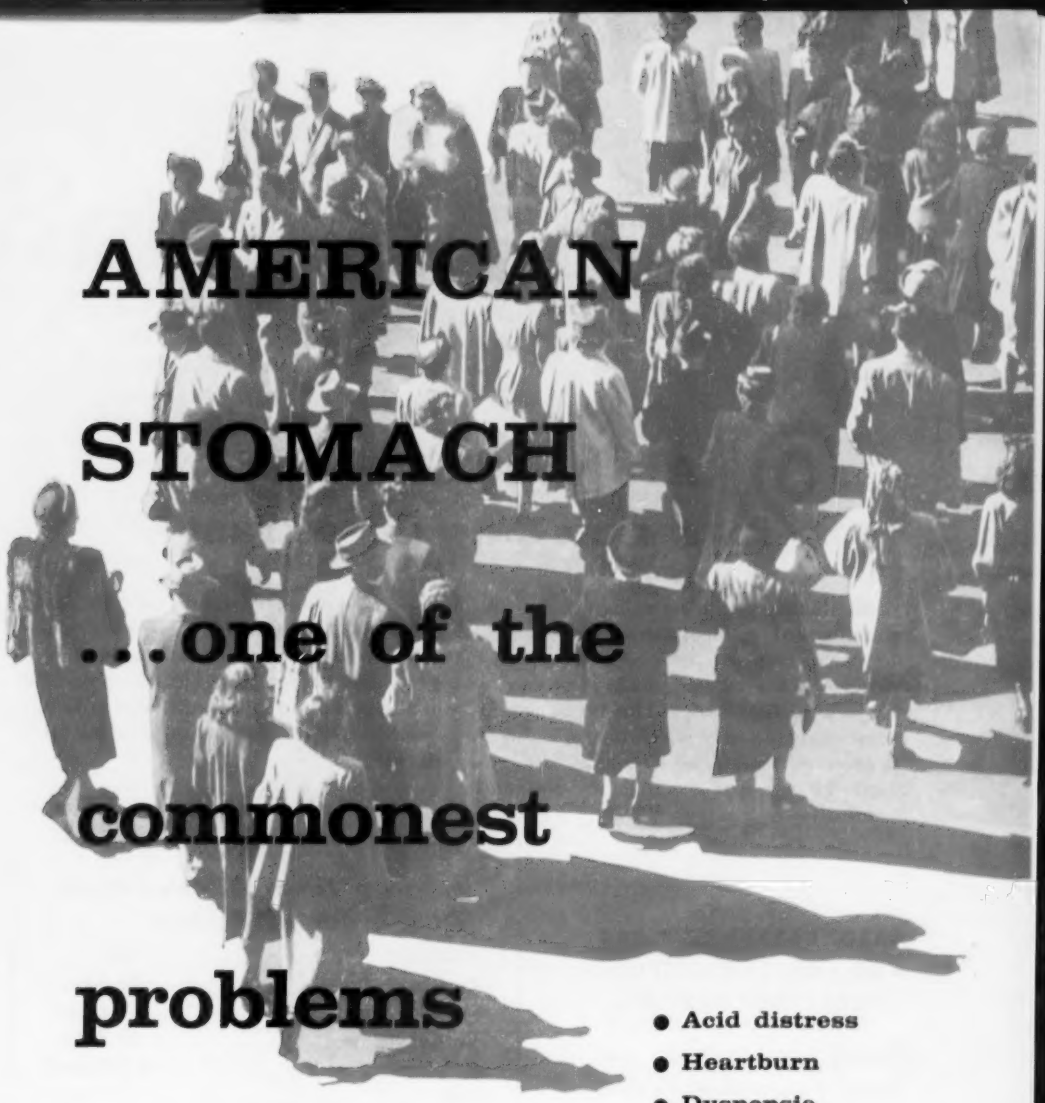

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Orange juice, fresh, ½ cup, Cereal, 1 oz., with whole milk, ½ cup, and sugar, 1 tsp., Bread, white, 2 slices, with butter, 1 tsp., Milk, nonfat (skim), 1 cup, black coffee.

Nutritive Value of Basic Cereal Breakfast Pattern

Calories	502
Protein	20.5 gm.
Fat	11.6 gm.
Carbohydrate	80.7 gm.
Calcium	0.532 gm.
Iron	2.7 mg.
Vitamin A	600 I. U.
Thiamine	0.46 mg.
Riboflavin	0.80 mg.
Niacin	3.0 mg.
Ascorbic Acid	65.5 mg.
Cholesterol	32.9 mg.

Note: To further reduce fat and cholesterol use skim milk on cereal which reduces Fat Total to 7.0 gm. and Cholesterol Total to 16.8 mg. Preserves or honey as spread further reduces Fat and Cholesterol.

Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: A Supplementary Food Composition Table for Dietary Studies. J. Am. Dietet. A.: Jan. 1957.

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Smith, Kline & French Laboratories, Philadelphia

1. Ende, M.: Am. Pract. & Dig. Treat. 6:710 (May) 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

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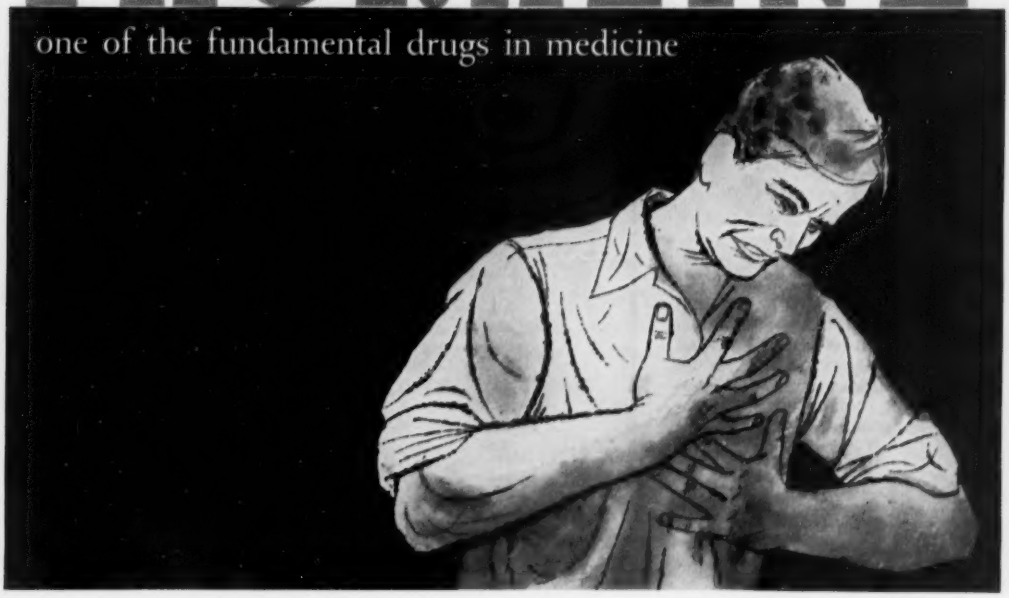

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1. Merrill, A.L., and Watt, B.K.: Energy Value of Foods...Basis and Derivation, United States Department of Agriculture, Human Nutrition Research Branch, Agricultural Research Service, Agriculture Handbook No. 74, March 1955, pp. 8, 9, 25, 32-43, 60-87.
2. McCance, R.A., and Glaser, E.M.: The Energy Value of Oatmeal and the Digestibility and Absorption of Its Proteins, Fats and Calcium, Brit. J. Nutrition 2:221 (1948).
3. McLester, J.S., and Darby, W.J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W.B. Saunders Company, 1952, pp. 189-190.

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Lemere, F.: Northwest Med. **54**: *1098, 1955.*

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Sokoloff, O.J.: A.M.A. Arch. Dermat. **74**: *393, 1956.*

3 "Of special importance is the fact that Miltown does not appear to affect autonomic balance—which in alcoholics is often unstable . . ."

Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. **17**: *19, 1956.*

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Borrus, J.C.: J.A.M.A. **157**: *1596, 1955.*

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Selling, L.S.: J.A.M.A. **157**: *1594, 1955.*

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1. Knoch, H.R., and Kirk, R.: Proclorperazine—A New Agent for the Treatment of Psychic Stress, in manuscript.

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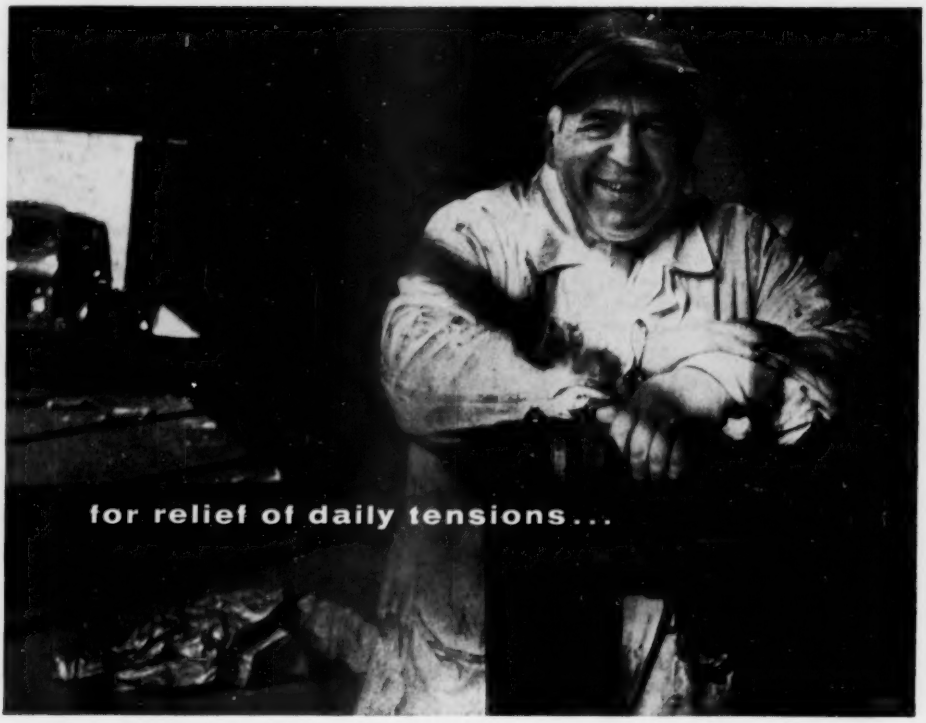

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*Ferguson, J. T.: J. Am. Geriatrics Soc. *4*:1080, 1956.

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